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 – Neurology Module

Announcer:
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, Neurology 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 Neurology 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 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 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 dissect all of the aspects of ARIA management that are expected to fall into the hands of neurologists to help guide practical clinical decision-making surrounding this unique adverse effect. To help with this discussion, I'd like to welcome Dr. John Toledo, Assistant Professor of Neurology, Nantz National Alzheimer Center, Houston Methodist. So I'm really excited to get going. And welcome, John, for joining us in this lively conversation.

Dr. Toledo:
Thank you, Jim, for having me here.

Dr. Galvin:
So let's spend some time talking about ARIA recognition and the management. And we're really going to focus on the role that neurology is playing here. We're going to do this by going through a case. So our case is of a 67-year-old man diagnosed with mild cognitive impairment due to AD, who presents discuss treatment options. He states he's interested in an amyloid targeting disease-modifying medicine. We know he's an APOE e4 carrier. He has hypothyroidism, hyperlipidemia, and an incomplete right bundle branch block. So the first question I want to pose to you is, should you be thinking about ARIA prior to therapy initiation?

Dr. Toledo:
Thank you, Jim. Yes, I think this is something we should always be thinking. And often when we discuss initiating new treatments, patients always have questions about what are the benefits like I will get, but also what are the risks. And they want, if possible, to know if we can predict or give them an idea of how likely one of these events can happen. One of the risks factors that we know about this patient, namely, being an APOE epsilon 4 carrier, can modify this risk. In the clinical trials that evaluated the response to aducanumab, lecanemab and donanemab, the absence or the presence of 1 or 2 copies of the APOE epsilon 4 allele were the strongest predictor of ARIA-E and also ARIA-H, even like 6 times higher risk of having ARIA-E in the case of, for example, lecanemab. And if somebody will present already at baseline, a high number of microhemorrhages, all the rates, and then presence of cerebrovascular disease, and we may see how they use the guidelines or recommendations that have been given, some of these may be some exclusion criteria.

Dr. Galvin:
No, I think you brought up a good point. When we think about the adverse event rate at the approved dose for the two approved medicines and for donanemab, which is still under investigation, what we know from the literature is that the estimated rate of ARIA-E is 35% versus 3% in aducanumab, 13 versus 2% in lecanemab, and 28 versus 1% in donanemab. When we look at ARIA-H, the rate of ARIA-H versus placebo in aducanumab 28 versus 9%, and lecanemab is 17 versus 9%, and donanemab is 31 versus 7%. And then each of the individual medications do have other prevalent adverse events, and they differ a little bit by the medication. So for example, in aducanumab, headache was the next most common adverse event in about 21%, over 16% seen in placebo. In lecanemab, infusion reactions occurred in about 26% of individuals, compared to 7% in placebo, and the studies published donanemab, nausea occurred in about 11% of individuals compared to 3% in placebo.

I think one other thing that, and I want to ask you this about this, John, ARIA-E and ARIA-H are also seen in the placebo group. So you know, when we're thinking about this, what - does this influence our choice of medication? Does it choose our choice of treatment? What do we discuss with the patients?

Dr. Toledo:
This is one of the challenging factors. Patients with Alzheimer's disease or MCI due to Alzheimer's disease, may have microhemorrhages. And one of the things that we won't be able to discern is if a patient that presents some mild ARIA-E or ARIA-H, if this was a positive by the same by the treatment itself. Because in the clinical trials, we are able to distinguish the treatment group and the placebo group and then we can compare the frequencies. But in the individual patients, we won't be able to discern, but luckily, we have like some recommendations. And once we see these imaging changes from the baseline scan, what we are going to do is use these criteria to guide our changes to treatment and how we monitor these patients.

Dr. Galvin:
So let's talk a little bit about the MRI criteria. Why don't you lead us through that?

Dr. Toledo:
Yes, and I think as we discussed, the one thing we want is to have like an MRI within 1 year, and then we are going to look for these which based on the current recommendations, are thought to be exclusion criteria, because they put a patient of - at higher risk of having complications during treatment with disease-modifying therapies. So as you can see, the presence of acute or subacute hemorrhage, having more than four microhemorrhages, if there is multiple areas of superficial siderosis, or if the patient has infarcts that are greater than 1.5 cm.

Another factor to consider is if there is like significant diffuse white matter disease or white matter hyperintensities, these patients might be also at higher risk of complications, and therefore might not be ideal candidates for this treatment.

Dr. Galvin:
Now, I mean for our neurology colleagues watching this, I mean, if you think about this, you know, on first pass, this might eliminate a lot of people from therapy, right? Because almost all our patients have white matter disease. Many of our patients with Alzheimer's disease have, you know, cerebral amyloid and, you know, amyloidosis, and so they do have some evidence of some microhemorrhages. So I think, as you mentioned, it's really looking for the burden of this going into the trial, rather than whether some of these things may be present or not.

So how would you counsel this patient on initiating amyloid beta DMTs, given his baseline ARIA risk? Remember, he's an APOE e4 carrier, he has some vascular risk factors, he does carry a bundle branch block that's known. How do we counsel the patient on this?

Dr. Toledo:
So one of the things is, and the nice thing is, we are gathering more and more information from the clinical trials, and we saw there, the numbers. And what we can tell them is that based on 1 or 2 copies, which in this case, we don't know, they are an increased risk of ARIA.

Another thing is ARIA is not a synonym of having symptoms. And there are different degrees of ARIA. And most of the cases or most of the patients who have radiological ARIA, around 80% of them don't have symptoms, so approximately like 20 to 22% of them are symptomatic. Also in the cases who have ARIA-H, without edema, those cases with isolated ARIA-H, the rate of symptoms is less than 10%. So on overall, the rate of symptomatic ARIA is less than 5%. However, once a patient present ARIA, they are going to be at risk of other complications and progressing. So this is something that this patient and his physician will need to discuss with them. And it will be best assessed based on the comfort level that patients and their loved ones have for risks.

Dr. Galvin:
So after discussion with the patient, they decide they want to start treatment with DMT. In this case, they're starting aducanumab. So

John, let me ask you what strategies should be used to mitigate the ARIA risk and maximize ARIA detection?

Dr. Toledo:
So I guess one of them would be to potentially increase the frequency. And they're like some recommendations to do some additional MRI scans, in addition to the ones that are done on a regular basis. And the other one is making sure that patients monitor and control their blood pressure. Because if they don't control their vascular risk factors, that may increase the baseline ARIA-H risk that these patients have.

I think another thing is to educate them well about the potential symptoms that might be related to ARIA so that if these appear, we can do an additional MRI to evaluate any complications.

Dr. Galvin:
Right. So let's talk a little bit about how we do this risk mitigation.

Dr. Toledo:
Yes, first, we are going to get a baseline MRI, and you will see that there are different schedules for the aducanumab and lecanemab treatment guidelines. And in the case of aducanumab, we are going to do it before the 5th, 7th, 9th, and 12th infusion. And in the case of lecanemab, it's going to be before the 5th, 7th, and 14th. And as we discussed, patients who are APOE epsilon 4 carriers, we may consider doing additional scans. And what we're going to be looking for is for differences between the baseline MRI and the follow-up MRI because there might be already some baseline changes that we need to consider and subtract when we evaluate changes. Also something to consider is that this is - the timing of the MRIs is based on the infusion visits, and the time between infusions is different. Aducanumab is on a monthly schedule, whereas lecanemab is every 2 weeks.

Dr. Galvin:
So this patient now presents for his 4th dose of aducanumab. At presentation, he reports a new onset dizziness, headache, and confusion. John, what would you do to evaluate this patient?

Dr. Toledo:
So most of the signs and symptoms that are associated with ARIA are going to be non-localizing and also not very specific. The most common ones are going to be headache, confusion, altered mental status, dizziness and vertigo, nausea and vomiting. And actually, it's some of the symptoms like headache, were also frequently present in the placebo group because this is a very prevalent symptoms or syndrome that presents in the population. Then we can also see fatigue, gait disturbance. And then vision disturbance and encephalopathy. And a small percentage of patients can also present epileptiform changes and seizures.

Dr. Galvin:
Yeah, I mean, you know, as a neurologist, or if thinking about the patient presenting in an acute care situation, you know, those first four symptoms, you know, a very, very wide differential diagnosis starts to pop up in my head, right? Particularly if they start describing like the worst headache they've ever had, you know, it's going to trigger a lot of things going on in my mind, and it might trigger some symptoms going on or ideas in emergency medicine physician's mind. So it's really important if you think about this, to be able to dive into the history and see is this person actually on a DMT? Or you might have a very, very different approach to your differential diagnosis.

So let's go back to our case, so we can follow what's going on. So this patient again presented for his 4th dose of aducanumab, and reported a mild headache, nausea, and slight dizziness. So on your evaluation, his MOCA score, Montreal Cognitive Assessment Score is now 20, which represents a 3-point decline from his prior visit. He has symptoms, and the timing of the symptoms appears to be in relation to his initiation of his amyloid targeting DMT. So, John, would you consider an out-of-sequence MRI in this individual?

Dr. Toledo:
Yes, I think this will be the next step until we – after getting the clinical history and potentially a physical exam. This will be our next logical step.

Dr. Galvin:
I agree with you 100%. You know, an out-of-sequence MRI should be ordered to rule out ARIA. So let's look at his images here. So we can see in the circled area, there's this hyperintense signal in the right temporoparietal lobe. So you can see the sulcal effusions here, okay. It's a small area, so it's less than 5 cm. This would meet the criteria for mild ARIA-E. So let's think about what are going to be the next things we're going to consider? What's running through our mind? John, let's talk about this grading. How do we do this?

Dr. Toledo:
Yeah. So here is a table where we're considering these two types of imaging findings. So we have the ARIA-E, which stands for edema

or effusion, and ARIA-H short for hemorrhage. And in both of these, we are going to look at the parenchyma and the sulci. And so here we have some examples where we can see this sulcal effusion, on the top left. And on the next two examples, the parenchymal changes where we see vasogenic edema in the occipitotemporal lobe and in the frontal lobe. And then we see microhemorrhages, which are those dark findings in T2*GRE SWI sequences, and those are parenchyma. The other finding in the sulci area is superficial siderosis.

So how do we grade them? And so here is a nice table. And there are some things that are similar that may help with our mnemonics. So ARIA-E, what we are going to look is for a mild presentation is one single ARIA that is less than 5 cm in its longest diameter. Moderate is when we have 1 between 5 and 10 cm, or we have multiple, but the largest of them is going to be less than 10. And severe is when we have 1 or multiple ones that are greater than 10 cm.

In terms of the ARIA-H, for the microhemorrhages, which are less than 1 cm, we are going to have 4 or less, then again, when we get to 5 to 9 new ones is going to be moderate. And the same number now 10; if we have 10 or more micro hemorrhages is going to be severe. And these should be compared to the previous baseline MRI. In terms of superficial siderosis what we are going to count is there is 1, 2, or 3 or more new focal areas. And so that's how we are going to classify their radiological severity.

Dr. Galvin:
Well, that makes it very easy because, you know, a nice chart really highlights, you know, how we're doing this. And is the type of information we're relying on our radiology colleagues to tell us but also we should be aware of it as the neurologist who's reviewing these scans and talking with the patient and the family.

So let's talk a little bit about some of the impact of ARIA on disease-modifying therapies. When do we suspend? So we have a little algorithm here. So if we see ARIA detected on the MRI, and the patient is symptomatic, as in this case, we have to decide, is this mild symptoms? Or is it mild ARIA-E? Or is it something more significant? If it's mild symptoms, and mild ARIA-E, on clinical judgment, we could continue therapy and monitor them very, very closely. But if they have moderate or severe ARIA of any type, or at least mild ARIA-H, then the recommendation is to suspend treatment and monitor them with monthly MRIs.

So John, when I'm looking at the MRI for these people that decided to suspend treatment, what am I looking for when I do these serial MRIs? Am I looking for different things, whether it's ARIA-E or ARIA-H?

Dr. Toledo:
Yeah, Jim, that's correct. So in terms of ARIA-H, we don't expect recreation or disappearance of deletions, so they are going to stay there. What we want to see is that there are no new ARIA-H lesions. This is completely different for what - how we monitor ARIA-E. In terms of a ARIA-E, the expectation is that over time, we - in the serial MRIs, we see a decrease and resolution of the symptoms. And based on the findings of the clinical trials, we expect that within 4 months, or 4 serial MRIs, we are going to see that approximately 80% of the ARIA-E cases are going to resolve.

Dr. Galvin:
And then we might consider resuming treatment at that point. So let me pose you a question now about this particular case. Would you continue therapy in this patient?

Dr. Toledo:
Oh, I think this is an occasion a patient that, after monitoring, we – will this be I think it's always good to involve both the patient and their family in the discussion, explains the risks and benefits. I always tell my patients I like to give them options and counsel them. But I think this might be a patient where if they feel comfortable with what has happened and the potential risk, to continue the treatment. But what we find based on the clinical trials is that there is a lower risk of having ARIA once the treatment is restarted.

Dr. Galvin:
So there is a little bit of debate on, you know, what should be done based on recommendations from different groups, we will see what's in the package insert. But we can also go to the literature and see that, in some papers, they give recommendations. So in this example, from Cogswell and the *American Journal of Radiology,* under mild ARIA-E, because they were symptomatic, their recommendation was to suspend dosing, and then once it's resolved, restart. But in other recommendations, it suggests that you could continue based on your clinical judgment. So I think it's important just to be aware that there are different recommendations, but your clinical judgment always is going to come into play. Right?

So let's go back to our case and see what's happening. One month later, the patient returns with severe dizziness, headache, and confusion. Should this person be referred to the emergency department?

Dr. Toledo:

Well, you might think we all agree that that would be our first answer, in this case.

Dr. Galvin:
Yeah, and I agree with you. So in the emergency room, an MRI is ordered. And if you don't even have to look at the picture of the MRI, you can just see that now the case is red. And we're thinking about what's going on. Right? And so remember, here's our baseline. John, take us through this. What are we seeing?

Dr. Toledo:
Yeah, so we've definitely, on the on the left, we have the baseline MRI. We don't see any significant ARIA findings. But then, as we look at the out of the cycle MRI that was done, we see like there is a diffuse ARIA-E and we can see changes clearly in the posterior area, as we discussed comparing with PRES and other conditions, so it might be that is more than what we see. But we see multiple areas with the larger area on the right occipitotemporal lobe that is greater than 10 cm. And I will say that it also there is some effacement of the sulci there. So we also see some mass effect there. So in this case, what we're finding here is that this will be a severe ARIA-E finding.

Dr. Galvin:
Yeah, I mean, I think when you look at this, it's quite striking, right? Because it's bilateral in the occipital lobe. But there's also frontal lobe involvement. I mean, this is a multifocal process going on. And I would agree with you, I think we have to think about what we're going to do for this person now. And so what do we do for this person, at this moment for this patient, you know, what's our recommendation?

Dr. Toledo:
So, I mean, this this case is based on a case report, and you can see the reference there, but there was also some a hypertension. So this patient was admitted to the hospital. And they actually was admitted to the ICU to manage the blood pressure. And so as part of the workup, in addition of the MRI, they ordered an EEG, and they saw some epileptiform changes, which is a more uncommon complication, or one of the more rare complications that we see. And so this patient received IV steroids, and also was started on an anti-epileptic treatment, because of the concern of seizure.

Dr. Galvin:
You know, and we had talked about this earlier, you had said that, you know, the incidence of seizures in individuals is quite low, it's less than 1%, which around 0.4% of cases. So, yeah, but this when it does happen, you know, obviously, we need to act upon it. Right? And so, I think you started to talk about this, what's the optimal management approach for this patient? And I just want you to go over this again, for the audience, because this is really important, because this is one of the more severe symptoms that someone could experience.

Dr. Toledo:
And yes, and there is like, no clear guidelines, or you don't - you won't find some recommendations on when to start the steroids or the optimal dose of steroids. But based on the case - there's severe cases that have been reporting – reported, what we think is that a short cycle like we use in other neurological conditions of a high-dose IV methylprednisolone for 5 days, followed by oral taper is considered in these cases of severe ARIA-E, like the one we saw. The other case - the other treatment indication here was in the setting of a patient who is a encephalopathic and has epileptiform activity, and anti-epileptic treatment was started.

Dr. Galvin:
So we have to think about when to discontinue, and we do have some prompts. So based on what we know from the aducanumab trials and what we'll continue to learn from the other trials that either completed or are ongoing, from a radiological perspective, patient has a macrohemorrhage to prompt to discontinue. If they have more than 1 area of superficial siderosis, which actually was the most common cause for study withdrawal from the aducanumab studies. And if they have more than 10 microhemorrhages since a treatment initiation - remember, this is where that baseline MRI is really important, because many patients might have microhemorrhages already. But if they have more than 10 new ones since initiation, from a radiological perspective, that would tell us it's time to discontinue the medications.

From the clinical perspective, if they have more than 2 episodes of ARIA, if they develop severe symptoms, or if they develop any medical condition that's going to require anticoagulation, and in this case, I think we have lots of evidence that there's severe symptoms because of the epileptiform activity seen on the on the EEG, so I would lean toward discontinuation. Would you agree?

Dr. Toledo:
Yeah, I agree. And one of the things that we may have not mentioned before is that, in general, there is some understanding, although we will need some more information, that patients on anticoagulation should not be started on an anti-amyloid disease-modifying therapy because of their increased risk of hemorrhage.

Dr. Galvin:
So let's go back and see what's going on with our patient. So he was started on levetiracetam and treated with IV methylprednisolone 1,000 mg for 5 days. What happened? A lot of the symptoms resolved, he showed a dramatic improvement on follow-up MRI, and he showed MOCA improvement over the next 6 months. Right? So a lot of the symptoms that were caused by these acute events resolved. And so we can see again, looking at his MRI, methylprednisolone was initiated. And you can start to see resolution of the ARIA-E here in the frontal lobe, and particularly in the occipital lobe. And as you mentioned, there was some effacement of the ventricle. And we can see now there's much less effacement. And so with resolution of ARIA-E and the cognitive symptoms, we continue to see improvement on his MRIs until it started to look a lot like his initial baseline MRI. And this corresponded to clinical improvement based on the symptoms that were noticed when he was experiencing symptomatic ARIA. So, you know, is that - John, is this what we would expect as a successful resolution? Is it the type of thing we're going to be looking for in our patients who are treated with DMTs?

Dr. Toledo:
What we would expect for the ARIA-E is that a majority of the patients that will be resolution of the finding. And we just need to suspend or stop the treatment and continue monitoring to see that we get resolution like the one we have seen here.

Dr. Galvin:
So, you know, finish it up for us. Take us through the - what's going on with this case.

Dr. Toledo:
Yeah, so as we said, patient was admitted to the hospital, and anti-epileptic treatment was started, patient got a 5-day bolus of methylprednisolone, as we discussed, and actually we saw the follow-up that we did, like an oral taper was started, that the treatment was discontinued, we saw the monthly MRIs that were done for monitoring. And we always – we don't treat MRIs we – or I always say we also treat patients and people so we want to assess how they are doing and how their cognitive and neurological exam changes during this time.

Dr. Galvin:
So again, I want you to check out our closing module for a multispecialty 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.

John, I want to thank you so much for participating in this. This was a great discussion. I think the audience really learned a lot about what to do in managing ARIA. Again, thank you so much.

Dr. Toledo:
Thank you, Jim, for inviting me to discuss this very important and timely topic.

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