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

Announcer Open:

Welcome to CME on Reach MD. This activity entitled Understanding the Fine Print: The Who, When, And What to Do About ARIA in Patients with Alzheimer's Disease, Primary Care 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 Primary Care 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 these specialties. In this module we'll focus on the how and why ARIA may present in a primary care setting, such that clinicians can be ready to identify and act on ARIA when it occurs.

Joining me today we have our primary care representative, Dr. Charles Vega, Clinical Professor of Family Medicine and Associate Dean at the University of California, Irvine School of Medicine, as well as Neurologist, Dr. John Toledo, Assistant Professor of Neurology at the Nantz National Alzheimer's Center at Houston Methodist.

So, I'm – I'm really excited to begin this conversation, uh, Chuck, welcome back and it's good to talk to you.

Dr. Vega:

Always a pleasure, Jim. Thanks for having me.

Dr. Galvin:

Alright, and – and John, great to see you.

Dr. Toledo:

Thank you for having me again. Always a pleasure to be here with you.

Dr. Galvin:

So, we're going to focus on a couple of things here today and um, uh, really thinking about the ARIA recognition and management, and focusing on the role of primary care. So – so, Chuck, lead us through this. So, what are we going to – what do we need to talk about when we're – we're meeting with our patients?

Dr. Vega:

Well, I – I really appreciate the changes to discuss this with both of you because this is the – we're rarely going to have a time where we

get to, you know, talk about, uh, disease modifying therapy for Alzheimer's disease, or mild cognitive impairment and the risk of ARIA, um, together like this. But hopefully we'll provide some, uh, some guide path today to what is expected in primary care. I think one of the – the main things that primary care needs to understand is, we are going to be very supported in encouraging patients to get the routine MRI monitoring. So, uh, that is part in parcel of this disease modifying therapy and so, uh, so therefore, and – and it's difficult for patients to always recall what their schedule is. They, you know, they rarely are, uh, dealing with, um, cognitive dysfunction as – as their sole disorder, uh, and they have multiple appointments, multiple, uh, ancillary studies to get then, so we have to help keep them on schedule. And we also have to be supportive of recognizing symptoms; one, preloading the information into patients as to what they could expect as symptoms of ARIA, so they know to make the call when they develop, uh, new symptoms or signs, um, and then, in addition, we respond to those as well. Because there's quite a range of symptoms. Um, most cases of ARIA, as we discussed, will not, uh, be symptomatic, but about a quarter will, and so therefore, uh, we're going to get into that in this discussion. And, again, how to, um, react appropriately to those symptoms, uh, is something that I think is best to manage between the, uh, neurologist, and the primary care, uh, provider, but we have a role to play.

Dr. Galvin:

Alright. Um, and I just want to point out again,um, is that, you know, all of these data are really being collected through this patient registry, which is really important because this is post-approval, um, and so, the Alzheimer's Network for treatment and diagnostics, or ALZ-NET, are – are really trying to get a capture of this real world data that's going to help, you know, providers across multiple specialties really understand ARIA and it's impact on – on patient care.

So, we're going to do this by talking about a case. Um, and I think that's always sort of the best way to – to have a lively discussion, and so let – lets meet our – our patient. It's a 70-year-old, uh, female with a history of MCI due to AD. She received her 5th dose of aducanumab 7 days ago. Now she comes to your office with an acute onset of headache and slight dizziness. Just quickly reviewing her medical history, she has type 2 diabetes, she has arthritis, hyperlipidemia, hypertension, um, and the MRI that was done prior to the 5th dose showed 3 microhemorrhages, which was unchanged from her baseline.

So, Chuck, let me pose this to you first. What are some of the clinical suspicions in this patient and what kind of information might you need to further that assessment?

Dr. Vega:

So, I think it's best to, uh, keep your differential broad at first. Um, we want to, uh, do a general headache assessment and that means getting a good history on the character of the pain, what makes it better or worse, particularly looking for, uh, red flags, uh such as headache that, uh, worse with exertion, or associated with any kind of neurological signs. Um, and then we want to get a – a pattern for headaches for her as well. Um, is this a – a typical headache she's had for a long time, um, or is this something that's new. And it sounds like, uh, like the ac – the onset is acute, which is automatically raising a little bit of a warning for me, um, and that she also has accompanied dizziness. So, those are two things that, um, that I'm concerned with right off the bat, but I – I don't jump right to the idea, well this is probably ARIA.

Dr. Galvin:

So, Chuck, at this point, might you reach out to your consulting neurologist, or I think, at this point are you still handling this yourself?

Dr. Vega:

I'd like to evaluate her. So, I'd like to – her to be seen, uh, right away. Um, I think the best thing would be – because that way we get some of the objective evidence as well, right? Um, we do a lot of telehealth these days but this one might be not the best case for – for doing telehealth. I really want to know how her blood pressure is doing. I want to do a neurological exam. And, uh, and so, uh, it, I think that for now I – before I, you know, make that call, I'd probably want to have her, uh, seen and – and just get a – a better sense of just how, uh, severe this headache is, and – and then put it on my differential diagnosis, start moving things around up and down, uh, based on that. And certainly, if I suspect ARIA, yes, I'm going to involve the treating neurologist.

Dr. Galvin:

Okay. Great. So, you're taking your history, tell me about the things that you are looking for. What are the signs and symptoms of ARIA?

Dr. Vega:

Right. So, it's not an unusual case for ARIA because headache happens to be the most, uh, significant symptom as – in ARIA. It's 47% of cases of ARIA have headache that are symptomatic. Now remember, only 26% of cases are actually symptomatic, 74% are not. She also has another classic symptom, which is, uh, dizziness. Uh, and dizziness as – as you well know, uh, that's a very broad differential

diagnosis. The fact that it's coming on together with a headache does make me believe this is probably more than say a tension headache, or a migraine headache, and some of the more common types of headache that I might see, even, uh, headache associated with a poorly controlled hypertension. Rarely do I see those two symptoms occur simultaneously, but I have seen it as well. I have – I – I have seen it – did – just because they are two incredibly common, uh, symptoms. Not just in neurology, but in general practice as well. And – but, you know, I think that if she developed more confusion, or an altered mental status, um, you know, that is – that's a much more concerning, um, uh, sign whenever you see it, uh, regardless of the patient's status with headache. And then you add in, uh, treatment with drug aducanumab, uh, it's going to be, uh, you know, very much a situation where, you know, now we take prompt evaluation to, uh, to do neural imaging and see what's going on.

Dr. Galvin:

Yeah. So, this going to be, as Chuck said, where bringing that patient in, getting a good history, doing a good physical and neurologic exam – nothing's ever going to replace that. Right Chuck? I mean, nothing's ever going to take away from actually laying hands on the patient and – and doing a good physical.

Dr. Vega:

Right. And if we're doing a telehealth appointment, especially if she has altered mental status, I mean, that's a clear indication where we're stopping that appointment and she needs to go directly to emergency department.

Dr. Galvin:

So, if we're going to talk about ARIA, we have to think about what the risk of developing ARIA and so – so John, lead us through this. So, what are some of the things that increase the risk of ARIA?

Dr. Toledo:

Yeah. So, if this – uh, we have now a – a experience through a different, uh, medications that we have gone through, clinical trials, and there are some other clinical trials that, eh, consider other treatments, and the one that, uh, especially stands out is the APOE, uh, genotype. So, it depends, eh, the number of, eh, APOE, um, 4 copies, uh, that the patient has and here we see that, although the 3 different treatments, 2 that have been approved, um and 1 that is still under investigation, they have different rates of ARIA-E. There is a clear increased risk as patients that are either heterozygous with 1 copy or homozygous with 2 copies of E4 and so this can increase the risk by 6 times of presenting ARIA-E.

And, if we would look at the percentages of ARIA-H which, as opposed to edema, is a hemorrhage, we will see also an increased risk with multiple copies. Also, when clinical trials have evaluated, or titrated doses, uh, greater those have been associated with greater risk, but at this point, once the medication has been approved, there is like a standard dosing. Also, having some baseline microhemorrhages in the MRI increases the risk and actually, in the recommendation guidelines, having more than 4 microhemorrhages can be considered reason not to start this treatment. Other aids and infarcts, or older hemorrhages, also increased the risk and might be considerations not to have this treatment. But something to consider also is that most of the ARIA-H and ARIA-E episodes are going to be asymptomatic, and most of the presentations are going to be mild. So, we have to have, uh, threshold – a low threshold to consider this, eh, in our differential diagnosis when a patient on these treatments has these kind of symptoms.

Dr. Galvin:

Yeah, I'm looking at this, uh, these lists of things that increase the risk and I want to focus on this first point, though, because, uh, Chuck, in – in clinical practice, you – you don't check APOE genotypes do you?

Dr. Vega:

Well, that – that's great. We're definitely thinking alike because this – this could be something of a paradigm shift. Right now, I don't know of any broad recommendations that call that we should be screening for APOE alleles. Um, even though it's fairly common – I think it's like 13% of, uh, adults carry, uh, you know, these alleles. So – so therefore, um, but does this change, uh, the – the way we initiate work-up. Is this something that we start doing in the broad population, maybe not, but what about patients who develop cognitive impairment. Uh, when we're thinking at that initial stage, I think about when – when I, um, diagnose, uh, cognitive impairment I send off a battery of labs, I get chemistries, I get thyroid levels, I get b12 levels, I get a CBC. And should I also be thinking about getting APOE with the thinking that many of these cases eventually are diagnosed as Alzheimer's disease and they could eventually be considered for treatment. So – so would it be more efficient in that initial battery to – to order APOE, to stratify patients, uh, risk of, uh, potentially getting ARIA on – on – on disease modifying therapy? That's a – that's a good question. I – I'd love to hear your opinion on it. Would that be valuable to you as neurologists to have that established when, um, when the patient comes in. Because the other thing with APOE is

that it's – it's fraught, you know, um, it has implications for not just the patient, but of course their family as well.

Dr. Toledo:

I – I think in my case I am considering testing when somebody, uh, wants to go forward with, eh, with this treatment.

Dr. Galvin:

Yeah, I think, uh, these are really interesting questions and we could spend just hours talking about this. I do think what Chuck said is true, it – it can start to change the way we're thinking about practicing. And I'm not sure the best recommendation at the moment, but – but I do think it's something we're all going to have to think about. So, lets now talk about some of the dosing and monitoring of the DMTs. John, take us through this because they're all a little different, right?

Dr. Toledo:

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

Dr. Galvin:

So, when does ARIA occur? Well, lets think about this a little bit. Um, so if we look at the relationship between ARIA and the exposure to disease modifying therapies, the fact is most ARIA events occur early phases of targeted therapies, and so the likelihood of ARIA occurs very close to when the initiation is, and the longer term that you've been treating, the less likely ARIA is to occur. So, that period of greatest risk with an approved DMT, we really want to make sure we're looking for ARIA. Um, so during aducanumab, it's going to be during the first 8 months of treatment. For lecanemab, it's going to be during the first 3 and a half months of treatment, about 14 weeks of treatment. And these are the two approved medicines. There's also an investigational drug, donanemab, and most ARIA occurred within 3 months. So, at the very least when you start these things we're going to be doing imaging at least for the first 3 months, depending on the age, and then going as far as 8 months if someone is on aducanumab.

So, lets think about this particular patient. After that 5th dose they're having symptoms. So, now we have to think about what we're going to do about this patient right here. So, we have symptoms of ARIA, we have timing of symptoms in relation to her dosing. Um, what do we think? What are we doing now?

Dr. Toledo:

Well, I think, eh, we should go forward with, eh, getting an MRI scan and due to be able to assess if – if this is something related to – to the treatment of, and something that we actually may need to modify our – our treatment and future steps.

Dr. Galvin:

Okay. So, Chuck, lead us through. Primary care, what do we do?

Dr. Vega:

Yeah, so, again, I want – it's – it's always hard to, you know, judge a case from a thumbnail, but, uh, it's definitely leaning that way, I agree, that we're going to, you know, require an MRI for neuroimaging. So, yeah, I would talk to neurology, and I would go ahead and order that MRI on a STAT basis and talk to whom I have to talk to so that they understand why it needs to be scheduled right away. And, if – unfortunately if that can't happen, sometimes it happens when I'm seeing a patient at 4:40 – if she came in at 4:45 p.m. and I called the radiology center and nobody is picking up the phone, then unfortunately she'd have to go to the emergency department. I'm not sure that clinically that I would say that that's my first option at this point, uh, without some – without more, you know, findings, I guess maybe on exam or something. She doesn't necessarily need to go to the emergency department this time, but – but yeah, just not being able to get the expedient MRI could be a reason to send her to the emergency department.

Dr. Galvin:

Right. Yeah. And I – I think – I think you've hit it on the nail. You – you have a plan, you have to figure out how to implement that plan and what's your plan B, C, D, etcetera, um, but also, you know, the severity of the symptoms really do come into play. We have – we have to really consider, like, how severe those symptoms are. Um, so what does that look like? Tell us, you know, clinically how do we say is this mild, or moderate, or severe?

Dr. Vega:

Right. So, I – I think that when we look at the – the category of more mild symptoms, these are the symptoms we manage every day in primary care, and I'm sure you as well in neurology. So, it's the headaches, the dizziness, visual disturbances. But I – to put a caveat in there, when patients complain about visual disturbances, is this due to the cataract that you've had a, you know, gradual, uh, diminishing of your central vision over the past 2 years, or is this new and acute. So, I think it's always good to, uh, to just get a little bit of background because it's those new acute onset of symptoms that's, uh, really concerning. I think infusion, of course, you're – you're focused on individuals here, uh, who have cognitive impairments, so – so they're at times going to be confused. But, again, we're looking for that sharp step-up, and it – again, maybe not just, you know, ARIA-E, ARIA-H, there either could be more significant bleed or something else that's going on and, hence the ner – the need for neuroimaging. Um, as you move towards more, uh, um, more severe symptoms, people can develop, uh, abnormalities with their gait, there could be falls. Uh, they could have nausea or vomiting from increased intracranial, you know, pressure, and by the time you get to, you know, partial blindness with agnosia and – and seizures, that's a very severe level and I think it's very clear those patients need to be seen in emergency, uh, immediately for appropriate care.

Dr. Galvin:

Yeah. I think, um, I think you laid it out really nice, is that the common things occur commonly and you're seeing them a lot, and it's the pattern and the temper relationship to what else is going on that's really key. But those more severe symptoms are – are really going to start to trigger, um, a response in you that, you know, you may need to activate emergency services much more so than for someone just walking in with a headache. Um, so I – I think that's a – that's a great discussion.

So, um, you know, go back to our case now. You have a clinical suspicion, how are you putting all this together based on what you're seeing?

Dr. Vega:

I – I think the most efficient care for this patient, because our – our emergency departments are very full so I try to use them judiciously, and – and because they're overwhelmed, honestly, that you may not always get the most expedient care, which is sad but true. Uh, and so therefore I think the – the best care for this patient is talk to the neurologist who knows her. And this is worth, you know, phone call over at the office so that they are aware, and then ordering that STAT MRI. So, now you want to be on the same page expecting to get results on an urgent basis, so, that same day, so that you can take action.

Dr. Galvin:

So, now John I want to turn to you. So, we talked about clinical severity, uh, lets talk about what we see on MRI.

Dr. Toledo:

So here we have this, eh, nice table that is summarizing, eh, the different type of imaging findings that we have. Eh, on the one axis and on the other axis, eh, we are quantifying the severity and one of the things, eh, we may have not mentioned before is that a CAT scan is not going to be able to identify these changes, and that's one of the reasons, eh, why patients who are, eh, not able to get MRIs are not considered for this treatment because we won't be able to assess or monitor them adequately. Going back to the table, what we see is two types of ARIA. So, this ARIA-E, which stands for edema, what we are going to see is white hyperintensity in this T2-FLAIR MRI, and what this is showing is the vasogenic edema. Another finding in the sol side between the different brain folds is effusion, and so what you will see is also, like, hyperintensity between them. The other type of finding that we have is ARIA-H, or hemorrhage, and again we're going to be looking at two spaces. So, one is in the brain or in the parenchyma where we will this microhemorrhages, which are less than 1 cm, and they look like these round or oval dark spots in light sequences that are T2-star GREs or SWI, which are especially designed to see the bleeds, and also we will see superficial sideroses, which is present in the sol side. And, so once we have this, what we are going to see is the extent of the number of lesions, and you will see that there is some numbers that are repeated here. So, 1, 5, and 10 is a number that is going to be helpful to remember. So, for the might edema, we will see one small, uh, side that is less than 5 cm in – in the longest, eh, diameter. For moderate, we will have either multiple sides or medium-sized sides, which is going to be 5 to 10. And a severe one is when we have at least one lesion over 10 cm on the scan with these edema or effusion.

For the microhemorrhages, it's going to be mild if we have 4 or less. Again, when we have 5 to 9 it's going to be moderate. And, when we have 10 or more it's going to be severe. And in terms of new events of superficial siderosis, it's going to be 1, 2, or 3 or more, and we

will see why we are doing – or going through this exercise because based on the imaging findings, and, eh, the presence of symptoms, it's going to be the way we decide how to act next or what we need to do.

Dr. Galvin:

Tell us what we're going to do. When do we stop these medicines?

Dr. Toledo:

Yeah. So, here what we have is, eh, first we have a, eh, got – gotten the history, we have examined the patient, we have the MRI, and so, let's go on the right side of this algorithm. So, we – we have a patient who is asymptomatic, but has ARIA, which is mild. In those cases we can continue the treatment and monitor monthly to evaluate for changes, and then based on resolution or progression, we – we will act accordingly. Then, we have the cases where there is a moderate or severe ARIA-E or ARIA-H, and here we are going to suspend the treatment and we are going to continuing doing monthly MRIs. The interpretation of the MRIs is going to be different for the – the edema or the hemorrhages. In terms of the hemorrhages, we are looking for no new events, or stabilization. So, we don't – we don't want to see new hemorrhages. But the ones that are there are going to remain. This is very different from the edema, where we expect that within 4 months, 4 out of 5 patients should have a resolution or disappearance. There is another situation where we have a symptomatic patients with mild symptoms and mild ARIA-E on the MRI, and in those case, the recommendations are not that, eh, clear and you need to use your clinical judgement. And so, you can continue treatment with monthly MRI or you may suspend, monitor, and then decide to resume treatment later.

Dr. Galvin:

Since this patient has mild symptoms, what path might she take?

Dr. Toledo:

Yeah. So, eh, in a patient with mild symptoms and might MRI, eh, in general, eh, the practice will be always, eh, in discussion with the patient and the family about the possible risk and benefit, eh, to continue the treatment and, eh, having a more, eh, intense, eh, monitoring with monthly MRIs.

Dr. Galvin:

So, let's continue with our patient. So, now she's doing the more detailed evaluation. Patient now is exhibiting some gait disturbances and you're trying to do some cognitive testing, and – and they just can't do it. They really seem to have this confusion. And now, while con – confusion may not always be a severe symptom, the fact is that you are noting that it's severe. So, what do we do now?

Dr. Vega:

Well, I might – I may get a call about this, or it certainly sounds like it's in my clinical evaluations, like, woah, this is more severe than I thought, you know, nobody mentioned anything about gait disturbances. In clear confusion, I'm trying to fill out, you know, fairly straightforward forms and assessments, um, this is – this is a downgrade. When would I not send a patient like this to the emergency department? But, particularly, in a setting of, uh, being treated with disease modifying therapy, uh, in that time frame where we know ARIA can occur, um, this is something that needs to go to the emergency department. We are not just talking about getting a, uh, diagnostic picture, but in hope – but possibly initiating prompt therapeutics as – as well, which could, you know, really improve her outcomes here, uh, before she has, um, you know, a – a major and more irreversible type of event. If you're in a resource-poor setting, getting and MRI after hours can be a, uh, true challenge. So, that's – that's another thing to consider and maybe have a plan, um, in the – and remember this is a – a rare case as – as, you know, 74% of presenting ARIA cases are asymptomatic, but um, but just have a – a plan for when this does occur if there should be these more severe symptoms. How the patient can be transported and evaluated at a center that can manage her adequately. Um, so, I – I think it's – it's, you know, it doesn't mean just because you're in a rural or very resource-poor setting that you can't use disease modifying therapy, but you want to think ahead and have a plan as well.

Dr. Galvin:

I agree with you. I think that these are things that we need to address more urgently. So, well, lets focus on now what we're going to do should this happen. Right? So, you know, does ARIA require additional treatments beyond just suspension or continuation? Well, I think it depends on what you're seeing. So, for those severe symptomatic cases, um, what would you do? Well, the recommendation is to use high-dose glucocorticoids, so I – IV methylprednisolone 1 g per day for 5 days, and this is followed by an oral prednisone, uh, treatment which could be tapered over weeks to months, depending on, you know, what you're seeing. And I – and I think this is something that could be done, you know, in the primary care setting, not the – maybe not the initial IV treatment, but for sure the – the longer term follow-up and the tapering. That all could be done in the primary care setting, wouldn't you agree, Chuck?

Dr. Vega:

Oh, for sure – for sure. So, when you coordinate there has to be a good handoff. Uh, usually these patients are going to be inpatients coming to the outpatient setting. But, no, I – I think that we certainly could manage a – a prednisone taper.

Dr. Galvin:

Okay. Now, this didn't happen in this particular case, but maybe for one of the more severe symptoms that have been found is – is either epileptiform activity on EEG or actual seizures, um, then the recommendation is this person is probably going to be on anticonvulsive, right? And – and – and, Chuck, this might be the case where, um, some primary doctors will feel very comfortable starting an anticonvulsive, and other ones are going to work in partnership with their consulting neurologist.

Dr. Vega:

Absolutely. I – I think that's the case. I – I'd certainly prefer, especially new case, uh, with ARIA, and it was severe enough to cause, uh, seizures, you know, having somebody touch base with the neurology is important. But this was, again, where if a patient is relatively stable, telehealth can be a good thing, both for consultation with neurology, but also for, uh, direct patient care as well.

Dr. Galvin:

Right. And the world has changed where we really have to think about how we're going to incorporate all these interesting, uh, changes to practice that, uh, you know, weren't really open to us, uh, you know, even 3 years ago.

So, um, this was a great discussion. It really was. I – I want to tell everybody who's watching to make sure you check out the closing module of the activity for a lively multispecialty discussion on the collaborative management of ARIA.

So, Chuck, I want to thank for this – participation in this conversation. Uh, I learned a lot, I hope you learned a lot, I hope the audience learned a lot.

Dr. Vega:

No, thank you. It was great. I really appreciate it.

Dr. Galvin:

And – and – and John, thank you for giving your expert, uh, opinions on the – from the neurology side. I think this really added to the interactive-ness of the conversation.

Dr. Toledo:

Thank you very much for – for having me here to discuss this very interesting topic.

Announcer Close:

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