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TIME OUT: A Case-Based Deep Dive into the Challenges of ARIA Management

Announcer:
Welcome to CME on ReachMD. This activity titled, "Time Out: A Case-Based Deep Dive into the Challenges of ARIA Management", is jointly provided by Medical Education Resources and Efficient, LLC, and supported by an educational grant from Lilly.

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Dr. Bateman:
Welcome to Time Out: A case-based deep dive into the challenges of ARIA management. I'm Dr. Trey Bateman and I'll be your guide today as we navigate real world case scenarios and explore effective strategies for ARIA management. The ARIA Toolkit is a multi-component curriculum designed to offer a comprehensive understanding of the complexities of ARIA. Throughout the curriculum, we'll engage in different interactive educational formats to equip you with the knowledge and skills needed to manage ARIA effectively.

In today's session, we'll take a case-based deep dive into ARIA management in the emergency care setting. By focusing on real world scenarios, we aim to build confidence in handling complex emergency situations involving patients receiving anti-amyloid antibodies. The curriculum is structured to ensure that every member of the care team can contribute meaningfully to patient care.

Let me introduce the expert faculty leading this multidisciplinary program. Again, I'm Dr. Trey Bateman, Assistant Professor of Neurology, Psychiatry and Geriatrics at Wake Forest University School of Medicine. Dr. Joy Snider, a Professor of Neurology at the Knight Alzheimer's Disease Research Center at Washington University School of Medicine, joins me in sharing her extensive expertise on Alzheimer's disease. We have Dr. Jerome Barakos, Director of Neuroimaging at Sutter Health in San Francisco, California who will provide critical insights into ARIA diagnostics and imaging. And Dr. Danya Khoujah from Advent Health in Tampa, Florida brings her experience in acute care management, ensuring that emergency care professionals are well prepared for real world scenarios.

Together, our goal is to provide a well-rounded interdisciplinary perspective on managing ARIA, enhancing your ability to deliver high quality care for patients with Alzheimer's disease.

All right. I'd like to welcome our esteemed faculty today. It's great to have you with us.

Dr. Snider:
Great to be here. Thanks.

Dr. Barakos:
Jerry, here. Thank you, and a warm welcome to everyone. It's really an honor to be here with this distinguished panel of experts.

Dr. Khoujah:
Thank you. It’s great to be here with the esteemed faculty.

Dr. Bateman:
So, we're going to be talking today about the importance of ARIA in emergent clinical scenarios. There's a lot of reasons to be talking

about. One is the increasing prevalence of anti-amyloid beta monoclonal antibodies. This is going to be something that our colleagues in the emergency departments across the country are going to be grappling with. There will be more frequent presentations of patients who either have ARIA or could have ARIA because of the expanded use of these drugs. This is going to be challenging in many of these emergency situations because ARIA can mimic many other acute neurological presentations, as well as making certain interventions that have become routine, inappropriate. So, for instance, if somebody presents with acute focal neurological symptoms and a normal CT scan in the past, giving TPA would have been a pretty quick decision, but that's maybe inappropriate for these patients. And so, it will require more careful consideration before some of those risky interventions.

And then, finally, this really brings to bear the importance of interdisciplinary coordination and requires collaboration between neurologists, radiologists and emergency department physicians, which is great because those are the folks that we have here today for this panel to talk across each of our specialties and the unique perspectives each of us have related to the management of ARIA. And it requires collaboration there to make informed decisions about treatment with anti-amyloid beta monoclonal antibodies, appropriate imaging protocol implementation within a health system, and how to best triage patients.

Dr. Snider:
So, first, we'll just go over a little bit about what are these anti-A-beta monoclonal antibodies. And they are the first disease modifying therapies that have been available for Alzheimer disease, so it’s a very exciting time. After 25 to 30 years of trying, we now have a disease modifying therapy in AD. What these drugs do is they bind to the amyloid beta peptide plaques and facilitate their removal from the brain.

We're not 100% sure how that works because very small amounts of these antibodies actually get into the brain, but they do seem to facilitate removal, probably through the vasculature, and you’ll hear probably more about that in a moment, because that's what relates to the ARIA. These antibodies are used in people with very mild impairments, so either what's called mild cognitive impairment, or MCI, due to AD, or mild AD. They're used in this setting because this is when they're effective and when the benefits outweigh the risk.

The most common adverse reactions include amyloid related imaging abnormalities, or ARIA, what we're talking about today, and infusion related reactions. These happen within a few hours to a day or so of the infusion. And then, some folks report headache. The two medications that we're talking about right now are lecanemab, which was approved in July of 2023, and donanemab, which was approved in July of 2024. The goal of these treatments is not to cure Alzheimer’s disease but to slow disease progression. So, they don't make anybody's thinking better but they do slow down disease worsening, as evidenced by measures of cognitive function.

Dr. Barakos:
So, let's look at some examples of this potential complication referred to as ARIA. As has been outlined, ARIA is an acronym that stands for amyloid related imaging abnormalities. So, with the mobilization of amyloid, we can see some transient changes in the brain. Now, it's very important to understand that this edematous process, the E form is where fluid will transiently leak out of vasculature, and we refer to that as an edematous process, and it's transient and it resolves without sequelae. At the same time, the vast majority of E ARIA, well over 70% with these agents, is going to be non-symptomatic, and that’s why you'll see that we have routine surveillance or monitoring MRIs taking place, because we want to know if the patient is developing this ARIA. Because if they do develop significant ARIA, that would be an important indicator that the patient should not receive additional dose at that next scheduled point. So, what we call a dose holiday or suspension depending on the severity.

Now divide ARIA into two types, the E type and the H type. E refers to the edema or effusion, depending on where the fluid is leaking. If it leaks into the brain parenchyma, that would present as an edematous process, or vasogenic edema as we have in the upper left hand corner. If it's leaking from the vasculature in the leptomeninges, this would present as a sulcal effusion, and you can see the blue arrow there pointing to an area of hyperintensity in the right frontal region.

Now, it's important to realize that we must use the appropriate imaging sequences to see these changes. For ARIA-E, we're looking for this hyperintensity, so we need a good quality T2 flare sequence to optimize conspicuity in identifying these areas of abnormality.

Now, the ARIA-H refers to blood product when red blood cells leak out of the vasculature. And when that occurs, again, that will present in the parenchyma or in the leptomeninges. When it occurs in the parenchyma, it will present as a lobar microhemorrhage. Typically, these punctate areas of hemosiderin deposition measuring 2 to 3mm in diameter. And when it occurs in the leptomeninges, that would present a superficial siderosis, as the example in the lower right hand.

Dr. Bateman:
Let's go through a case presentation and sort of think through this. Here, we’ve got a 72-year-old woman who arrives to the emergency department with her husband. She presents with a headache, aphasia and confusion, which began about 2 hours ago. Notably, during the history, you find that she has a history of mild dementia due to Alzheimer's disease, and the husband mentions she's on a treatment

but can't really remember the name of the therapy.

Now, let's have an interdisciplinary time out here and discuss this a bit further. Danya, is your emergency department equipped to optimally triage these folks receiving anti-amyloid beta monoclonal antibodies?

Dr. Khoujah:
Well, I don't think we have caught up with the times yet because the numbers of patients are so slowly increasing. There is no protocol in place on how to triage these patients, but I think that that's going to be an important way for us to improve our detection and recognition of ARIA, is to have a system in place to one, know that patients are on this medication, and then, two, alarm the clinical care team to make sure that they are aware that this patient is on the monoclonal antibodies to recognize that ARIA might be in a differential and that that might actually need a different work up or a different approach when they come in with symptoms that may concern us for a stroke or a bleed, or a hypertensive emergency.

Dr. Bateman:
Are there changes that you feel like need to happen in the emergency department to help better recognize these folks when they come in?

Dr. Khoujah:
I think one thing is first to talk about this a little bit more. We need to educate our physicians, our advanced practice providers, our triage nurses, about the anti-myeloid treatment. We basically can say, hey, you know what? There is a new medicine that's being given. It's being given to some of our patients, not a lot, but it is there and it will continue to increase. And that's where our education comes in, is emergently evaluating patients who are on anti-amyloid treatment for any neural complaint. The same way we do that for stroke assessment, right? When we say the word stroke, hey, we think this person might be having a stroke, everybody's running to the bedside.

Let's stand there and say, hey, this patient might be having ARIA, and run to that bedside and evaluate them by a medical professional who is comfortable with that and is aware of what that means.

And on the flip side of it, we need to have some sort of safety blanket, so it's not just dependent on whether the triage nurse did ask the patient and figured out what the correct medications are. Let's add another layer. Any person we see in the emergency department with a neural complaint, whether we're talking about headache, confusion, seizures, new onset numbness or slurred speech, or whatever we think of a stroke-like symptoms. We need to actively ask them, hey, are you getting any injections or infusions arranged by your neurologist? They might not know exactly what it is, but at least that's a tip off that would lead us in the right direction.

So, I think also, recognizing that patients with Alzheimer's are not necessarily in that classic dementia box that we think of, where they're floridly confused and they cannot manage their own affairs because that's not the reality. And that is not the patient population that's going to be getting those medications. And finally, I believe Joy was talking about that before, is that patients that are going to be on these medications, maybe we can give them a card, encourage them to have a photo of it on their phone. We take photos of everything, right? Take a photo of this and favorite it, and tell people, hey, when you see care, show them this picture. Or give them a little wristband that says that you are on this. We do that for ICDs, we do that now in our hospital for patients who just had, like, major surgery. Why don't we do this for a medication like this?

I think that at the end of the day, if we think about this outside of the box, we're going to be able to pick up a lot more on these patients, but it's only going to happen if we sit together and brainstorm those ideas of how can we recognize these patients, because that's going to be first step to physically figuring out how can we take care of them.

Dr. Bateman:
Really great points on how this fits together with so much of the overall care system around patients with dementia, what we even – or mild cognitive impairment, and what people think about when they see Alzheimer's disease. So, absolutely fantastic points.

When these folks show up to the emergency department in places that have neurology available for consultation, when should they be brought on board?

When should that consult happen? Joy, do you have thoughts on that?

Dr. Snider:
So, I think consulting neurology early if you can is a great idea if you're at a hospital that has neurology around. We have neurology residents who go see these patients, so it's great for them to see the patients early and a great educational opportunity. If you don't have neurology around, you don't have a low threshold to contact the patient's neurologist. Sometimes patients know who that is, sometimes they don't. So, again, trying to have that available in the EMR, trying to have patients have contact information is really key.

But it's important to consult early because, as Donnie pointed out, some ED physicians are very comfortable with this and some are not, so we want to be there to service back up and to help them out as best we can. But consulting when there is a focal neurological complaint for these patients is important, again, to sort out, is it ARIA, is it something else. And that's really key to do that as early as you can.

Dr. Bateman:
Let's move on with the case and see how this blows through the care scenarios. So, just as a review, this was a 72-year-old woman on an anti-amyloid beta monoclonal antibody who presented to the emergency department with headache, aphasia and confusion. It began 2 hours prior. The discovery of that monoclonal antibody might come up as the husband said, right? She's on some new drug for Alzheimer's disease. And then it turns out that you find out it's the infusion drug, and you're aware that those have these potential new side effects that you have to worry about. You found out that she received 2 doses, so she's early on in the treatment, and the most recent was 6 days prior to symptoms beginning.

Blood pressure, here. A little bit elevated at 170/95, but all of her other vital signs are stable and normal. On physical exam, you find that she's an oriented a person, but is confused about time and place, has some mild slurring of her speech with mild ataxia, and difficulty on her finger-to-nose test. And all of these, importantly, are not present on a baseline exam from that recent neurological visit that she might have had. Because she came in with acute onset of neurological symptoms, an NIH stroke scale was done and it's a 5. That gives you a little bit of a sense of the severity of these symptoms and where they line up.

Dr. Khoujah:
So, what are important differentials to consider? It's important to recognize the clinical symptoms of ARIA because they can be quite variable. ARIA symptoms can be things like headache, confusion or altered mental status, dizziness, nausea and vomiting, gait disturbance, visual disturbance. Rarely, patients can come in with a seizure or that seizure can be progressing to a status epilepticus. The differential diagnosis can be quite wide, but in the emergency department, we always think of the worst first. So, we think of things like strokes, infections and PRES, and we think usually acute ischemic strokes when somebody comes in with an acute onset of hemiparesis with facial paresis with visual changes, with dysphasia, with dysarthria. And in this case, the patient does have some visual changes, so we might actually think of a stroke as the differential of her presentation.

Well, the real question is, well, how prevalent are ARIA and how often do we need to think about them in our clinical practice? Well, let's take a step back and look at the studies and see how often ARIA was present in those patients. So, looking at these numbers overall, 3 to 6% are going to be symptomatic and less than 1 to 2% are going to have severe or serious symptoms. So, overall, a pretty small percentage of patients who are getting this medication. And this is going to be mostly during the first few months of treatment because that is when patients are most at risk for ARIA.

Dr. Bateman:
Joy, what information do you think is crucial to know about this particular patient at this stage of the workup?

Dr. Snider:
Well, it's really important, as with all things in neurology, to really just hone down on the history, and find out important things like when was last infusion? How many infusions have they had? And get at the nature of the symptoms. And as Danya pointed out, what other things are going on? Have they just started a new medication? Did they just have a bad night's sleep for the last 3 or 4 nights? So, any other things that could trigger delirium. But just really important to get the good history, know what's happening clinically, and what their history is with the medication. And the other point, not particularly relevant to this ARIA conversation, but we're seeing a lot of headaches in people as an infusion reaction. So, again, another thing for our ED colleagues to be cognizant of. We probably would get an MRI even if we did think it was an infusion reaction. But having ARIA within a day or two of an infusion, particularly your first one, is not typical. But always also something to think about.

Dr. Bateman:
And then what about CT scans? Right? They're really common to get when folks come in with these neurological changes. Jerry, CT scans? Can that help us at all in these cases?

Dr. Barakos:
That's a great point because obviously CT imaging is our gold standard when a patient hits the ER with the altered neurocognitive status or any concern about the head. You get a CT. And so, that's a great question. In this setting, of a patient who maybe we don't know they're on an anti-amyloid agent, or maybe we do, what role will CT play?

Well, fortunately, we have about 20 years of experience now in the use of these anti-amyloid therapies in trials, and what we've noted – because many times, we'll have a patient who's being treated has symptoms, goes to the ER, gets a CT, and then we can compare it

with MRI that's done subsequently.

And as you can imagine, when we look at these changes on MR, of course those subtle areas of ARIA-E are going to be invisible on a CT without a doubt. So, mild ARIA-E, whether it's sulcal effusion or parenchymal edema, we know that's going to be very hard to see on a CT. But if it tends to be moderate to severe, yes, we'll be able to see those subtle areas on CT of the gyral swelling, sulcal effacement, maybe some parenchymal hypodensity. So, yes, the CT can play an important role.

In regards to the ARIA-H, of course those blood products are too small to be seen on a CT, so the CT is going to be of no value for ARIA-H. But really, it's going to catch the more severe forms of ARIA-E. Now, that brings up the point of, as has been described here, MR can be very helpful. Let me just stick with the CT for a second. For example, if you think the patient is having a stroke, if you do a stroke CT protocol, what we're doing a CT profusion with CT angiography, it turns out that ARIA will not give you a perfusional deficit, just like on MRI. It will not show restricted diffusion or cytotoxic edema. So, if you do your CT stroke protocol and you've got a perfusional deficit, well, obviously you have a stroke. If you don't have the perfusional deficit, that doesn't help you. It could be ARIA, it could still be a stoke. It doesn't differentiate the two.

If one does an MRI, if you see the restricted diffusion, obviously you're dealing with a stroke. If there's no restricted diffusion, then either you don't have a stroke, or that can be ARIA if there is associated T2 flare hyperintensity. So, again, these will be important topics we'll touch on in a little greater detail. But yes, it kind of changes the whole dynamic for everyone caring for the patient because we've got this new entity, the ARIA-E, that we have to consider. And we can't simply assume it's ARIA-E until proven otherwise, so at the same time we don't want to miss a stroke, so we're going to have to walk a very fine line where treating a patient with ARIA with a TPA would lead to a very bad outcome. So, we have to make a very accurate decision based on the available information that we'll touch on.

Dr. Bateman:
So, back to our case. After a consultation with the neurologist on-call, the patient does get sent to MRI to evaluate for ARIA versus other neurological causes of these symptoms. And here we've got the MRI finding.

Dr. Barakos:
So, in terms of that MRI finding, how is this graded in terms of severity by the radiologist? Now, on the package insert, we have kind of a standard grading scale, and it's simplified. It's kind of rules of 5. So, for the ARIA-E, we are measuring the areas of abnormality and if it's less than 5 centimeters, it's considered mild. Moderate would be 5 to 10 centimeters and greater than 10 centimeters would be severe. So, it's kind of an easy paradigm one can use. Just rules of 5 to break it into mild, moderate, severe. However, there's one pearl that I find the majority of radiologists, even when they're very familiar with ARIA, fail to capture and it's the following:

You do not measure simply the area of hyper intensity. If you do that, you will frequently, grossly underestimate the stage of ARIA, which can mislead the clinicians caring for the patient. And you can take a moderate or severe, and if you mismanage it or miss measure it, you can claim it's mild and they may get dosed through which would be a very negative outcome.

So, here's the point. If we take a look at the middle case, for example, where we can see the hyper intensity, which is primarily a sulcal effusion. If you compare that exam to baseline, you'll see that all the sulci related to the more anterior portion of that temporal lobe are gone. They have normal signal intensity, but there's gyral swelling and sulcal effacement presenting as an altered morphological pattern. So, the bottom line is, when you measure ARIA, you have to keep measuring until you get to normal brain. Not just intensity, but normal morphology. You've got to see normal sulci, normal gyri. And you also have to do it in a 3-dimentions. So, for example, in this case that's moderate, if it starts going up the parietal lobe into the high parietal convexity, you need to measure in that oblique pattern.

So, long story short, simple, don't just measure the hyper intensity. You've got to measure until you get to normal sulci and normal parenchyma, because oftentimes, most of the vasogenic edema is basically just swelling without hyper intensity.

Now, let's turn to the ARIA-H measurement. For ARIA-H, remember, patients have been excluded from treatment if they have more than 4 microhemorrhages, or more than either 1 or 2 depending on the agent, more than 1 or 2 areas of superficial siderosis. Those patients have been excluded. They typically, are not treated with these agents because they potentially would have very high risk of having complications because they probably have significant underlying cerebral amyloid angiopathy. So, when we are counting now, ARIA-H findings, these are incident findings. These are new micros or new areas of siderosis. So, that's what we're reporting to the clinicians. And again, it's pretty much rules of 5 here. If you're 4 or less, it's mild. So, if you had, let's say, one area of superficial siderosis, it's going to be considered mild. Two, moderate. More than 2, severe.

For the micros, if you have less than 5, that's mild. Between 5 and 9, that's going to be moderate. And 10 or more, that's going to be severe. So, basically again, relatively easy to remember those cut offs. And again, it's imperative that we relay that information to the clinicians because if they're having moderate or severe ARI-H, that would be indication that the drug should be held.

Now, we have a lot of good resources that have been put together by the American Society of Neuroradiology, and the link is down at the bottom of this slide. It provides templates for imaging reports because remember, as outlined earlier, the clinician doesn't want a report that just says unremarkable scan. The question for the clinician is, did you look for a subtle area for sulcal hyper intensity or did you count the micro hemorrhages?

So, that's why it's imperative to have these templated reports, which really forces the radiologist to answer the questions. And we found, in many cases, even radiologists don't understand what ARIA is. If the report, their template, says is there ARIA? We're very good at just-in-time learning. One can quickly kind of look, OK, what is ARIA? Oh, it's an area of hyper intensity. As a radiologist, I can certainly look for that. Or a microhemorrhage, I can certainly count those. But we need to know that we have to be looking for those and that can be the value of a templated report. And at the same time, we have to know and explain to the physician the extent of these findings. Because as we've seen in the grading scale, it's important to note was there just two new microhemorrhages compared to baseline or were there 5? Those can be important implications. And this is kind of important for radiologists because normally we don't count micro hemorrhages. It hasn't been really, an important aspect of neuroimaging, but here you can see in the management of these patients, it actually is a very important topic.

Now, at the same website we also have information for imaging protocols. As we've discussed, you want to use appropriate T2 flare-weighted sequences. Oftentimes people ask, well, Jerry, should we use a 2D or a 3D? Answer there, for example, is it doesn't matter as long as it's reliable, robust and repeatable. You want the best quality imaging. So, the last thing we want to do is ask someone to, let's say, do a 3D where they have trouble with it and there's inappropriate or incomplete water saturation, and it leads to false positives and false negatives in identifying ARIA.

So, the bottom line is, for the T2 flare, whatever you do in your institution, a good quality T2 flare, whether it's a 2D or 3D. For the susceptibility weighted scans, most of us nowadays are using SWAN, or susceptibility weighted imaging. GRE T2-star is fine. It turns out that this grading scale is based historically on the GRE T2-star, and that's because, for the last 20 years, when these studies were being performed, we had to use kind of the lowest common denominator for scanners across the world. So, we would use the current ADNI recommendations at that point in time. So, it is based on GRE T2-star, and yes, people say, well, Terry, we're going to see more changes with susceptibility weighted imaging. And that's certainly true but we tend to be a bit conservative. I think most institutions will either do a GRE or SWI or both, but we'll still use the same count numbers and really leave it to the discretion of the clinicians caring for the patient whether they would kind of incorporate the idea that, yes, there's going to be more sensitivity with the susceptibility weighted sequence, so maybe we'll let a few more micros in.

Dr. Bateman:
Alright, so back to our patient who is a 72-year-old woman who came into the emergency department with a headache, aphasia and confusion, and found to be on anti-amyloid beta monoclonal antibodies. Symptoms that began about two hours ago and just got her MRI, and Jerry will tell us what we're seeing, here.

Dr. Barakos:
Very good. So, this is her T2 flare, and obviously, quite a dramatic MRI where we see a lot of signal abnormality. First point to be made, this certainly is not a vascular distribution. We're clearly not dealing with a stroke. This is going to be more in keeping with an encephalitis or cerebritis. Maybe even PRES. We don't know, but it's not a vascular distribution. Now, this is a T2 flare. We looked at the DWI. There's no restricted diffusion, so that tells us, OK, there's no cytotoxic edema, so we're basically thinking some sort of nonspecific edematous process. If you give gadolinium, it'll be negative in the setting of ARIA. If this was, let's say, a severe cerebritis or meningitis, you typically may have some leptomeningeal enhancement.

So, important points on MRI, your DWI in the setting of ARIA will be negative and you will not have significant contrast enhancement. So, in brief, we look at this scan and the question here is what is the classification or the grading of this ARIA-E? And I think, as you've heard me say earlier, it's important to measure all the way to normal sulci. And on this scan, there probably is not a normal sulcus visible, except for maybe in the frontal. So, this unfortunately, would be a very high grade of ARIA. So, greater than 10 centimeters and so this would be a severe example of ARIA-E.

Dr. Snider:
So, now that we have our patient in the ED and they're symptomatic, and we've got an MRI which shows us severe ARIA-E, this is probably a patient we're going to admit to the hospital and we're going to consult our neurologist in the hospital. We would probably consult a vascular neurologist. This patient would come through the ED with concerns for stroke. But we want to make sure this is a vascular neurologist who knows about ARIA and ARIA management.

So, the things we would do in the hospital? Typical things we do for a neurology admission. We're going to very closely monitor their

neurological symptoms. This can be challenging for cognitive symptoms for sure, but we will try to do the best we can to monitor those. And then, we're going to maybe even put them in a neurological ICU or a step-down unit. If they're unstable, this lady sounds pretty stable, so she would probably be admitted to a neurology service. And then, we're going to consider treatment options. And we really have some experience with ARIA from these clinical trials, but not very much. And as we've said, only about 1 to 2% of people on these drugs will get symptomatic ARIA. What we generally use, because this is what we used in neurology a lot, are high-dose steroids. There's growing evidence, this is an inflammatory reaction, an inflammatory type of cerebral amyloid angiopathy, or CAA, so it is very reasonable to think it would respond to high-dose steroids.

These patients are people that have a very mild dementia, so they may not have much impairment at baseline, but certainly they are at higher risk for delirium and at higher risk for steroid-induced confusion and delirium, so that's something we want to be careful to watch out for. Often, we follow this with an oral taper. This is all really still very empiric. There no clear protocols for how to do this. You can try, if the patients are not this severe, to treat them on an outpatient basis with oral steroids, for example. But we don't have guidelines for this and they remain at high risk for delirium and steroid-induced psychosis, so that can be challenging as well. Generally, these patients do improve. Perhaps not necessarily if it's severe over 3 to 5 days, but usually over the ensuing weeks and months.

We didn't mention, but many times in these cases with ARIA-E, there's also ARIA-H that you will see in the same area. Sometimes you don't microhemorrhages until after the edema clears up a little bit, but that can also happen. So, we would certainly, in this case, stop dosing and not resume. In milder cases, we might resume. This would be a conversation with the patient and their loved ones. In many of our patients, the patients are very excited to resume treatment and really want to do it, so you do have these conversations to really emphasize that if it is moderate/severe, there is risk for recurrence and there are rare cases where people do not recover. So, the patients and families need to be aware of that.

So, this kind of goes through our thought process. Again, this is not yet written in stone because we are very early in this process. But basically, the management strategies are, we do want to have a good baseline MRI and certainly, in our practice early-on, when we were getting MRI's from a variety of radiology centers, sometimes the baseline was not so great, and sometimes we didn't figure that out until we got the monitoring MRI and realized that there were 5 to 10 microhemorrhages there that were probably present on the baseline, but weren't detected. We do the MRI monitoring, and again, we might do an emergent one if the patient has symptoms, and then we detect ARIA. So, if it's asymptomatic and mild, we can continue dosing. We would monitor again in 4 weeks just to make sure that the ARIA was not progressing. If it's symptomatic, or it's severe or moderate, we would probably hold dosing for at least a month. So, it would be two doses of lecanemab or one dose of donanemab, then repeat the MRI, and then see if the ARIA-E is resolving. And then, again, if it's moderate and the symptoms completely resolve, we can consider resuming treatment. But the symptoms don't resolve, or the ARIA-E is severe, we would probably not resume treatment.

We would not resume treatment if someone had a macro-hemorrhage. So, had a hemorrhage that was larger than a centimeter. If they had more than one area of superficial siderosis, we would likely not resume. If they get more than 10 new microhemorrhages since we started treatment, or if they have ARIA more than once, if they have it twice. Again, the anticoagulant is part of the appropriate use recommendations, but it's not an absolute contraindication, so we would have a discussion with the patient and family about the increased risk from that.

But this is a guideline. I think we expect these guidelines to change as time goes on and we get more information, so stay tuned.

Dr. Bateman:
Well, we have the answer, in this case, that this patient presented with severe ARIA. But what about the instance if this patient had had, while on an anti-amyloid beta monoclonal antibody, rather than the MRI showing ARIA, what if she had presented with an acute ischemic stroke?

Dr. Khoujah:
Looking at the insert itself, it says serious intracerebral hemorrhage greater than 1 centimeter have occurred in patients treated with this class of medications. And that gets really tricky because when patients are coming in with concerns that they may have a stroke, the first thing that we're going to reach out to the fibrinolytic, or what we think of as TPA or TMK, right? And because of that increased risk of hemorrhage, current recommendations state that acute thrombolytics should not be administered in patients who are on anti-myeloid antibodies until the safety evidence of their combined use is available, which is not where we are right now with our data. And that's why that should be a case by case consideration and a discussion with the patient and the care team, the interdisciplinary care team; the neurologist, the primary care doctor, the patient, the patient's family and the specialist who is also managing whatever condition when you've got anticoagulation, whether it's BBT or PE or a-fib or one of these thousand things that patients are going to randomly come in with that's not related to this medication and might need anticoagulation for.

Dr. Bateman:
So, the question about what happens when people come in with an acute ischemic stroke, has been a topic of conversation since these drugs were approved. The appropriate use for recommendations, as Joy said several times, are conservative recommendations right now, and centers have varied with how they are implementing the practical realities of navigating competing risks for patients. So, earlier this year, Dr. Saver from UCLA presented some examples of how UCLA is operationalizing their code stroke pathways in individuals with Alzheimer's disease on anti-amyloid beta monoclonal antibodies. And so, this is not the way everyone is thinking through it, but it is a rational, thoughtful way to think about how you evaluate and consider risks in folks with acute ischemic stroke on these antibodies.

So, if you look at this provisional pathway they have, it's sort of broken down by how frequently this presentation occurs, the key features of the presentation. And then, what do you get in terms of CT and CTA angiography. And then, how useful is an MRI, MRA, or perfusion weighted imaging going to be in that case. And then, finally, what are the considerations for thrombolytics in in those cases.

The complicated situation is this 10 to 20% of strokes that come in with a moderate to severe deficit – so, it's not in that low NIH, too mild to treat, but there's also not a large vessel occlusion. So, what you may be seeing is something that's a medium vessel occlusion or lacunar infarction. And so, in that case, you're not going to see a large vessel occlusion on CT or CTA, and MRI/MRA and perfusion imaging is going to be absolutely essential to correctly identifying the mechanism of disease that's going on.

If there is an accessible medium vessel occlusion that your interventional neuroradiologist feels like they might be able to get in the neuro Cath lab, they would send them straight there. If there's not an accessible medium vessel occlusion, that's where this really comes down to a very careful discussion after an MRI about what disease process that you think is going on. And the fact that we don't really have a lot of great data on this would be something to carefully consider, talk through with patient and family, and document very carefully before moving along with thrombolytics in that case, especially in light of the fact that there's these published recommendations that say don't do this. And so, this is something that I think each individual institution and stroke service is hopefully having conversations about upfront well before this is a question in the emergency department. But this is a reasonable and thoughtful way to try to think through how you would approach this in the real world.

So, what are the challenges that arise when a patient on anti-amyloid beta monoclonal antibodies presents with an acute ischemic stroke? How do those imaging findings influence the decision on whether you might administer thrombolytic therapy, like TPA or TNK, in a patient at risk for ARIA-H?

Dr. Barakos:
Well, let me start with the imaging perspective, there. Trey, you did a beautiful example outlining the role of imaging, and I think the take-home message there was, typically in our institutions will use CT imaging as the first-line for stroke. So, you call stroke protocol, bing, you have specific time you need to get the CT head, CT angio, CT perfusion. And that happens very quickly, and we get that in a short period of time. If that shows you have a stroke as evidenced by large vessel occlusion, or you have a significant perfusional deficit, you've got a stoke. Then, the clinician can ascertain how we're going to manage that. Are they going to lab? Are we using TPA, et cetera?

So, first branch point. If your stroke protocol is positive for a stroke, you've got a stroke. However, if it's negative, you could still have a stroke with a normal perfusion area and no evidence of a large vessel occlusion. So, what you're going to do is, at this point, you could have a stroke, or you could have ARIA. Your decision is going to be based on the clinical information, and that's going to be imperative. Is the patient on anti-amyloid therapy? What is their stroke scale? You have to put all that together.

But you can see that MR imaging plays an important role in that secondary phase, because if your CT stroke protocol is negative, that's where you get a rich kind of tapestry of information from the MRI. Do you have T2 flare hyperintensity in non-vascular distribution? Well, obviously, that's not a stroke, that's going to be ARIA most likely, if the patients on an anti-amyloid agent or could be cerebritis, et cetera

Number two, what does your diffusion scan show? Might it show a small lacunar infarct? Or, bingo, you've got your diagnosis of stroke, and you're not worried about ARIA. However, if your diffusion is negative and you see flare hyperintensity that's consistent with ARIA, you can make that diagnosis. So, the summary seems to be, MRI can play a very important secondary role to provide additional information to help us feel more confident that, A: we don't have a stroke, and B: yes, this represents imaging findings in keeping with ARIA.

Dr. Snider:
Yeah, Jerry put it very nicely. We really depend a lot on the imaging findings here. But I would just synthesize that the discussion around thrombolytics specifically is based on a single published case, and hence that there are additional unpublished cases of someone who presented, possibly with ARIA, and received TPA and had a fatal outcome with lots of microhemorrhages, lots of edema. So, it's difficult

because we don't have a lot of data, I think as Danya said, but at this point, I would be very reluctant to recommend TPA in somebody who's on these medications. Again, you can't say you would never do it because it really depends on the severity of the stroke, the evidence for stroke, the need for thrombolytics, how the family and patient feels about their future after this stroke if it could not be reversed. But it is a very scary scenario. It may also come up for people with cardiac events, and that's something we also need to start thinking about and again, making sure that our colleagues are aware of.

Dr. Bateman:
Our counseling when people are making the decision to go on to these monoclonal antibodies is largely that you probably won't be eligible for treatment of stroke. In this case, I think that's probably the right counseling to folks. And then, if there are complicated extenuating circumstances, that the discussions happen acutely when that happens. But it seems much safer to prepare people for the notion that it's very unlikely in many of these cases they would receive treatment for that ischemic stroke with thrombolytics.

What about some challenges? I imagine there's unique things that community and academic centers might face regarding patients on monoclonal antibodies against amyloid beta, who present with an acute ischemic stroke. Certainly, MRI is a precious resource, and I've had many instances where my colleagues don't love me trying to get a lot of MRIs from the emergency department.

Dr. Snider:
I think it's important for our community emergency departments to be able to reach out to specialists for this. So, in our area, we have a spoken hub network where the Community EDs can reach out, but that's not true everywhere. So, it's really important to empower the patients with all the identifying things we've talked about to make sure they communicate this to the ED physician, so they know to reach out to somebody with some knowledge about this if they're out in the community or not familiar with these medications.

Dr. Khoujah:
Just like Joy and Jerry said, it's very important to make sure that the ED team is able to identify, one; being on this medication, and two; what MRI to order and ordering that correct MRI if it is available. And that is where having a working relationship with a radiologist, with a neurologist, to connect with them, whether they are at their center or outside of their center. Because reality is, patients will not go back to the hospital where their neurologist is. Patients are going to show up to the freestanding emergency department next to their house when their neurologist is definitely not working there.

And reality is, for the time being at least, community emergency departments are not going to have a protocol in place to specifically address patients coming in with ARIA. So, it's going to fall on the independent emergency physicians and the neurologists in their community to come up with how they're going to manage that and frequently contact each other until there are protocols in place. If the uptake of these medications continues, then protocols will show up eventually because the numbers are going to go up. But the reality is, at this point in time, with the number of patients on these medications, community EDs are not going to have a protocol in place just yet.

Dr. Bateman:
That brings us to the end of today's session. I'd like to thank our expert faculty for their valuable insights and for guiding us through the complexities of acute ARIA management.

Dr. Snider:
Thanks. This was a terrific discussion, and really appreciate everybody's viewpoint. And thanks to the audience for being here.

Dr. Barakos:
Really a great pleasure and a lot of fun.

Dr. Khoujah:
Thank you for having me, and it was definitely a great time learning from my colleagues. Hopefully our audience enjoyed listening to us as much as we've enjoyed recording this, and they've learned as much from us as we've learned from each other.

Dr. Bateman:
I'd also like to remind you that this program, Time-Out, is just one part of the ARIA Toolkit curriculum. We encourage you to stay tuned for the other modules, which will provide additional opportunities to deepen your understanding of ARIA across various clinical scenarios and settings.

Thank you for being part of this collaborative effort to improve the care and outcomes for patients with Alzheimer's disease.

Announcer:
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