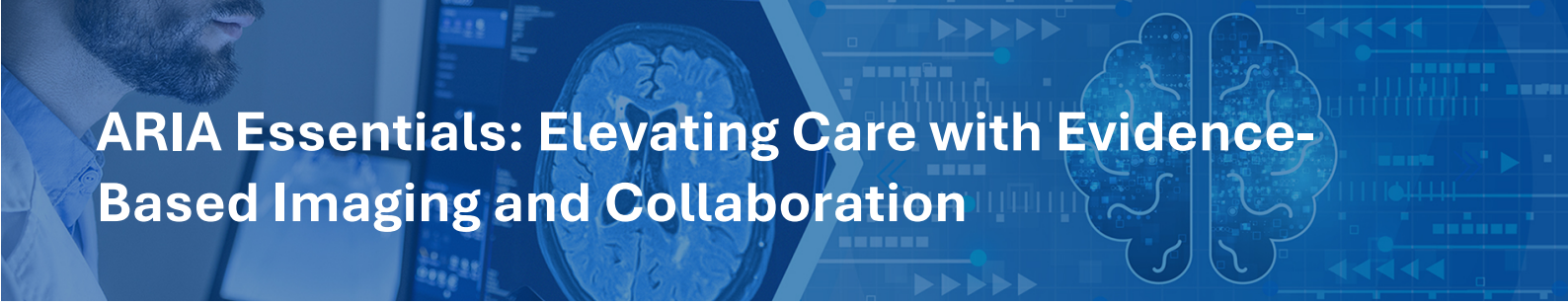

ARIA Essentials: Elevating Care with Evidence-Based Imaging and Collaboration

INTERDISCIPLINARY PERSPECTIVES

Alireza Atri, MD, PhD: Hello, this is ARIA Essentials: Elevating Care with Evidence-Based Imaging and Collaboration. I am Dr. Alireza Atri. I'm a cognitive neurologist and the chief medical officer for Banner Research. This is an educational activity that's supported by an independent educational grant from Eli Lilly.

Petrice M. Cogswell, MD, PhD: Hi. My name is Dr. Petrice Cogswell. I am a neuroradiologist at Mayo Clinic in Rochester, Minnesota.

Anton P. Portseinsson, MD: My name is Dr. Anton Portseinsson. I'm the William B. and Sheila Konar professor of the psychiatry, neurology, neuroscience, and Medicine at the University of Rochester School of Medicine and Dentistry. I also direct the Alzheimer's disease care research and education program here at the university, and singularly focused on the care and study of people with Alzheimer's disease and related dementias for the past 30 years. Pleasure to be here.

Maria Vittoria Spampinato, MD: Hello. This is Maria Vittoria Spampinato. I'm a neuroradiologist at the Medical University of South Carolina in Charleston.

Dr. Atri: Learning objectives for today are, by the end of this educational initiative, we'll be able to better identify the pathophysiological features that put patients taking anti-amyloid monoclonal antibodies at potential risk ARIA, which is amyloid related imaging abnormalities. We are going to be able to apply standardized MRI protocols and grading scales to optimally monitor for detection and assessment of both severity and the nature of ARIA in patients who are receiving anti-amyloid monoclonal antibodies. And we are going to be able to integrate best practices for interdisciplinary communication to enhance coordination among radiologists, neuroradiologist, prescribing clinicians, including dementia specialists, neurologists, geriatricians, psychiatrists, and others in the management of ARIA.

What is ARIA, amyloid related imaging abnormalities? In the word, it says imaging. ARIA is an imaging finding. It's an MRI signal changes that are thought to represent vasogenic edema or fusions, and also cerebral microhemorrhages or other heme products that were actually first reported in the context of bapineuzumab treatment because this was an experimental plaque lowering monoclonal back in 2009. The thoughts about ARIA are that there's a common mechanism of leakiness of exudate, fluids, or blood through stiff and leaky blood vessels.

This can happen in the context of amyloid plaque-reducing antibodies as there's almost a traffic jam that can occur in the perivascular spaces and with the monoclonals and antibodies affecting them. What are the different types of ARIA? There's the edema effusion kind, and there's the hemorrhagic kind. It's really, really important that particular sequences are used to identify ARIA. You'll hear more about appropriate sequences for those. For ARIA-E really it's a T2 FLAIR, is really, really important. Oftentimes you'll see here in the image, you'll see areas of either parenchymal edema, that's bright signal, or you'll see effusions within the sulcus, and this may also be associated with gyral swelling.

There are various regions that can be involved. Basically, multiple loads can be involved at times. We'll learn about ARIA grading, the imaging severities, but oftentimes autoregulation tends to break down much more in the occipital lobe. All things being equal, occipital predominance tends to occur more, as well as parietal and temporal and also frontal, less so in the cerebellum in the brainstem.

The vast majority of ARIA tends to be actually not symptomatic, tends to be an imaging finding, and that tends to be also transient, but in some cases, it can also be severe and cause symptoms, and we'll talk a little bit more about those.

The other kind of ARIA that we see is the ARIA-H. This is, again, deposition of heme products. Most often you see dots around the brain from leaky blood vessels or microhemorrhages, small that are definitely less than one centimeter. Occasionally you could also see laptomeningeal or peel hemosiderin deposition also thought to be called superficial siderosis. Rarely, and this is the dreaded consequence would be a cerebral macrohemorrhage. For the most part, what you see are microhemorrhages and occasionally superficial siderosiss. These are best seen on basically T2 star sequences, whether they're gradient echo or SWI. SWI tends to be a bit more sensitive and gradient echo is less sensitive, but maybe more specific. Sometimes, it can be difficult to decide whether there's a blood vessel there or whether this is a cortical subcortical, microhemorrhage.

Back to the hypothesis, what causes ARIA? I mentioned that over time almost any person with Alzheimer's disease in the later stages will have deposition of amyloid in the blood vessel walls. Over time, the blood vessel media can actually be replaced by deposition of Aβ40 oftentimes. As this happens, the blood vessels become both leaky and also stiff. In the context of plaque-lowering antibodies where they may have a large shift of amyloid plaques being removed from the brain, that could actually cause a traffic jam in some ways. That's the hypothesis in the perivascular areas, causing even more antibodies to back up also causing potentially inflammation in the media, and making the blood vessels more leaky for exudates causing edema or effusions or potentially even blood products.

There tends to be an overlap with a phenomenon we'll see called cerebral amyloid angiopathy-related inflammation. This is a phenomenon condition that is seen in patients with CAA sometimes where one can get almost a fulminant reaction of edema. There's a thought that there may be some common mechanisms there. How often does ARIA occur in the context of plaque-lowering antibodies? Now remember, all the studies are different. One plaque lowering-antibodies not the same as the other. The inclusion criteria in the trials were different. Monitoring schedules were different, dosages were different.

Generally, what was seen is that there were surveillance and scheduled MRIs to catch these imaging changes during the course of the trials. Depending on one's risk factors, depending on, as you'll hear from my colleague, Dr. Porsteinsson whether they had *APOE4* or not, or whether they're homozygous or heterozygous, the risk was a bit different and the rates were a little bit different. Generally, ARIA-E tends to occur anywhere between, let's say about 10% to even upwards of 40% of persons in these studies.

The most important thing is that appreciate that they were caught on imaging. In the cases where ARIA was caught, almost in all these trials, about three-quarters were not symptomatic. They were caught at a stage where there were just imaging abnormalities, but not symptomatic. As far as grading the ARIA, as far as the severity goes, we'll learn that the size and the number of foci, et cetera, matter for ARIA-E. Again, the vast majority in trials, imaging-wise were mild or moderate. They were not severe large areas of ARIA, and only a minority of cases were actually, as I mentioned symptomatic. Depending on the trial, whether it was 1 out of 100 or 1 out of 200 or so individuals, sometimes because of the ARIA actually had to seek medical attention.

ARIA-E is something that over time should resolve with management. ARIA-H, because it's actually blood products that have now been fused, we're looking for stabilization. In that case, we also have a

grading scheme as far as emergent number of microhemorrhages or superficial siderosis, and also protocols and suggestions about how to manage them with repeated imaging and or dose holds.

Oftentimes, the treatment has to be individualized even though there's guidance. Sometimes there can be holds of treatment. In trials, there were also cases where people were sometimes resumed at longer interval or lower dose. It's also important to note that ARIA can recur. It could also evolve even though infusions are being held. Having a very close clinical and also routine imaging follow-up is really, really important.

Most ARIA is not symptomatic, but when it was symptomatic, oftentimes the symptoms were things that were quite general and things that could actually happen in daily life. Now, in some cases, they were a little bit unusual. Maybe there was a new headache or a different kind of headache. Things like headache, confusion, dizziness, nausea, imbalance, those things can actually occur to older patients and patients with Alzheimer's disease in daily life, less so visual changes, for example. Again, it's really important to have these discussions with patients and families about what symptoms can occur and to communicate with the team about the symptoms, not to ascribe a symptom due to something else and say, "Oh gosh. Well, I've had a bit of a pressure and pain in the back of my head here, but it's because I have a new pillow."

It's important to discuss with your clinician and clinician team that, "Hey, I have this, what do you think?" For the team to go through the appropriate triaging and assessment. Now, occasionally, I would say rarely people can actually have severe symptoms of ARIA. This could mean out of control blood pressure, seizures. People have had status epilepticus, focal neurological deficits, and even macrohemorrhages and even deaths have occurred and in the context of clinical trials and even clinical care. Oftentimes there have been some extenuating circumstances. Maybe they received, for example, a thrombolysis. Even in the course of treatment, there is an uncommon and rare chance that symptoms can be severe and also lead to death. Knowing the risks, discussing the risk, having appropriate patient selection is really, really important.

Dr. Portseinsson: Dr. Atri has covered what is ARIA. A couple of points that I'd like to make in particular is the fact that ARIA tends to happen early in the course of treatment, particularly within the first three months, and certainly within the first six months. Usually, if you have ARIA-E, it resolves within eight to 12 weeks. How do you minimize the risk of ARIA? You minimize risk of ARIA by careful patient selection upfront. What we do know is that the highest risk factor for developing ARIA on one hand can be a medication and the speed of titration of the medication.

There is a difference between the different antibodies, but others are very much patient-related. *APOE4* status, in particular, if you are an *APOE4* homozygote, that is you have two copies of the *APOE4* gene, your risk of developing ARIA-E in particular as well as ARIA-H, a little less is significantly increased. We see up to half of people that are *APOE4* homozygotes that develop ARIA, less so with the heterozygotes. That of course means that those that carry *APOE3* or *APOE2* have lower risk. In addition to APOE, cerebral microhemorrhages as well as superficial siderosis. Any kind of extravasation of heme products increases risk.

Also, any evidence on an MRI that suggests that there's a meaningful CAA present. Furthermore, things that have been connected to ARIA risk are antithrombotic use. It is age, history of prior strokes. There is debate whether there's a difference for the different ethnicities or races as well as sex. There's not strong evidence that there's a big difference there, as well as cardiovascular risk factors. Particularly poorly managed cardiovascular risk factors such as high blood pressure that is not managed, diabetes that is not managed, hypercholesterolemia as well as smoking. At the start, let's make sure we pick the patients that have lower risk of developing ARIA and those that may have risk

that they are aware of them. It is part of the treatment guidelines to check *APOE4* status before starting treatment. We do that at our center. We don't mandate it, but we strongly encourage it because I think it is important for the patients to know what their relative risk is, and also important for us to know because our monitoring may be that much more diligent.

Spend some time upfront on picking the right patients, be aware of what the risk factors are, and remember that those risk factors can change during the course of treatment.

Dr. Atri: Thank you, Dr. Porsteinsson. I completely agree, and again, this is evolving ARIA as more data comes forward. I know in clinical trials, there was, as far as antithrombotic use, they had different inclusion-exclusion and according to appropriate uses, certainly, maybe standard dose aspirin would be okay, but maybe not dual. I think the data for anticoagulation is still accumulating, but both the proper use recommendations and many others will exclude patients on anticoagulation at this point until there's further development.

Of course, we know that the risk with thrombolysis can be also high. Keeping in mind all the things you mentioned, *APOE4* copy number, underlying CAA and vascular risks, the exposure of the drug, the timing, managing blood pressure, and having a very informed, supportive discussion with the patient and caregiver about those things is really, really important.

Dr. Spampinato: A takeaway message is to really know the patient's history and review the chart carefully as important information should not be missed. As radiologists, it's very important not only to recognize ARIA early but also to differentiate it from other lookalike conditions. In fact, there are a number of imaging findings that overlap between ARIA and other disease processes.

For example, cerebral amyloid-related inflammation, posterior reversible encephalopathy syndrome, and even stroke. In fact, with CAA-RI, on MRI, we'll find spontaneous sulcal effusions, vasogenic edema, and also microhemorrhages, and superficial sclerosis or findings that we see in ARIA-E and ARIA-H. In PRES, we'll find findings of vasogenic edema that are usually in the posterior brain in asymmetric distribution, but also hemorrhages, including microhemorrhages, intraparenchymal hematomas. In patients with stroke, depending on the specific type of stroke, we'll find findings of parenchymal brain edema as well as subarachnoid and intracerebral hemorrhage.

How do radiologists make the appropriate diagnosis? Whenever we see findings on MRI, they may look like the first thing that we do is try to find out more information about the patient. The first step is finding out if the patient is on anti-amyloid immunotherapy. That information may be available in the chart, or if this is a new patient, we may have to call someone and find out.

We also want to learn more about the clinical context as some of these conditions such as PRES occur in certain clinical scenarios. For example, in the case of PRES, it'll be hypertension or immunosuppression. Finally, there are also imaging findings that can be important. Specifically, diffusion MRI can help to differentiate acute infarct that will have decreased diffusivity from ARIA-E, which will not. Taking into account all these aspects would help us with the differential diagnosis.

Dr. Cogswell: I think that's an excellent overview. I think highlighting the two steps of the first, the history is the patient on an anti-amyloid immunotherapy, and then the second, the common overlap between ARIA and acute ischemia, and the importance for MRI in those scenarios and specifically diffusion-weighted imaging.

Dr. Atri: Yes, that's really, really important because if someone comes in with potential symptoms, then really, I think a CAT scan would not be sufficient, correct?

Dr. Spampinato: Absolutely. A CT scan will not be appropriate for this diagnosis and an MRI will be needed.

Dr. Atri: How do we balance those things in the sense that, I know for years and years we've been trying to speed up the process of time is brain when it comes to stroke and some of the emergency departments, et cetera, don't always have access to vascular neurologists? I guess, what are the main considerations here and suggestions that you have that we can, I guess, get information out to our colleagues about this overlap and how it's really, really important to be able to distinguish potential ARIA from actual ischemic stroke?

Dr. Porsteinsson: I do believe that the prescriber, the clinician that is prescribing amyloid-directed treatment has a significant responsibility to make sure that every attempt is used to inform your colleagues that this is the way it is. We can do that in many ways. You can, for example, put a banner maybe on your e-record for the individuals that are on monoclonal antibodies targeting beta-amyloid. You could possibly, if that's not something that is available to you, put that into the drug tolerability/allergy section, and warn about the use of thrombolytics or of anticoagulants, and make sure that the patients that are on these medications have cards that they can give to their treaters. For example, if they come into the emergency room or their family has those cards available. It's critical to make sure that all the other providers that are involved are aware of this.

For example, it's our responsibility to be clear when we're asking for MRIs of this nature, that it is for the reason that we aim to treat this individual with amyloid antibodies so that the right sequences are secured and the radiologist or preferably neuroradiologist, is guided towards what they're looking for. Their job is hard if they don't have that information. I do think that that is critically important for the clinicians to take a certain degree of responsibility, and also make sure that the patients and families are aware of the importance of communicating this.

Dr. Atri: I agree with everything you said, Dr. Porsteinsson. I think in the real world we're trying to get this information out, and sometimes despite the best laid plans, the communication isn't quite there. They may go to the emergency department that doesn't have access to, in a different system, for example, that may not see that. Maybe the patient and care partner or caregiver are unable to or don't have the discussions about the patient being on the medication.

I want to ask Dr. Cogswell about the importance of I guess closed-loop communication in this setting particularly. Where one may not have other images et cetera, but the symptoms may look like stroke. They may be going down a stroke alert pathway. I'm interested to hear from you two how you would approach that closed-loop communication with all the different carers involved including the ED.

Dr. Cogswell: We've talked about education on multiple levels, and I think to have the closed-loop communication as well as I guess close up a lot of the holes in the system, that it's important to have as many people along the way educated, from the patient to the ED provider, to the neurologist who may see the patient as a consult in the emergency department to the radiologist. If one of those people along the way brings up the fact that this patient is on anti-amyloid therapy, then I think that changes the direction of care.

That makes then the radiologist perhaps reading a head CT, aware that, "Oh, this looks like new edema. What is my differential? What is the need to recommend a brain MRI?" I think by educating on multiple levels we can hopefully close up those holes and make people aware of the possibility of ARIA in these patients. Another important point is that when these patients are started on therapy, they need to have a center that they go to to get their regular brain MRIs. It's also important I think that

when they have an acute onset of neurologic symptoms, that they're at a center that has after-hours MRI because that would be as we're saying a limitation in their care pathway if that is not available.

Dr. Spampinato: We often encounter this scenario where the patient comes in as a stroke code, and they first undergo the CT but at some point along the way, somebody typically has recognized that there was a banner somewhere, or there was some information about anti-amyloid therapy. At that point, it's important that a radiologist be in the loop. It would help if the study indication clearly states, listen, we learn that the patient is on treatment, and that will help us inform their diagnosis. Otherwise, we can go the wrong path and recommend contrast and basically, not nail the diagnosis right away.

Dr. Atri: I think the concern here is that when patients are on therapy with these monoclonal antibodies and if they have ARIA or maybe even microhemorrhages, that anticoagulation may increase their risk, and particularly I think there are some cases where patients have received thrombolytics and have had poor outcomes, including unfortunately death in a few cases. This is something that really has to be deliberated, I think. I think the other part of that is, even if one knows that they're on, let's say, a monoclonal for this purpose, really thinking about what may be the other options other than thrombolysis or whether it really would be indicated, that bar being higher.

If it's a large vessel occlusion, potentially if there's access to go to a direct mechanical thrombectomy, for example, may be an option, or thinking about if a patient is symptomatic, whether actually the symptoms are related to maybe anything that you're seeing on the CTA may be a different territory, for example, or maybe the NIH stroke scale isn't high enough. Those are nuances that I think that potentially could even lead to disagreement on management. How does one think about standardizing reporting and what are the best practices to think about MRI protocols and also reporting and communication protocols?

Dr. Cogswell: Yes, great. I'll start with a brief overview of some of the appropriate use recommendations for anti-amyloid immunotherapies, including appropriate selection of patients for therapy. The appropriate use recommendations discuss components of the appropriate diagnosis, clinical stage, and biomarker characteristics of patients who are candidates for therapy. Also, the assessment of risk-benefit in determining appropriateness with risks including the presence of *APOE4* carriership, as well as findings on the pretreatment brain MRI, particularly those of cerebral amyloid angiopathy.

As we've discussed, another consideration for deciding to put these patients on therapy is the current or potential future need for anticoagulants or thrombolytic therapy, which, as we discussed, is contraindicated for patients on anti-amyloid immunotherapies.

Appropriate use recommendations and FDA labels also provide schedules of brain MRIs to be performed during the course of therapy. This includes brain MRI within one year prior to the initiation of therapy, which is used to evaluate for exclusionary findings as well as provide a baseline for future comparison. There are also multiple brain MRIs needed during the first year of therapy to evaluate for asymptomatic ARIA. If ARIA is identified, a monthly brain MRI is required until the resolution of ARIA-E and stabilization of ARIA-H. Additionally, a brain MRI may be warranted if a patient presents with new neurologic symptoms.

When a patient comes in for these brain MRIs, it is helpful for the relevant findings to be summarized in the form of a reporting template. Through the American Society of Neuroradiology, as well as other societies, dedicated reporting templates have been suggested for use at the time of what we'll call an

AD therapy enrollment exam or that pretreatment baseline exam, as well as the MRIs performed to monitor for ARIA.

The relevant findings to include in that AD therapy enrollment or baseline exam are those that are used to evaluate patient eligibility for treatment, which are based upon risk for ARIA. Those include the presence of microhemorrhages, superficial siderosis, extent of white matter hyperintensity, as well as infarcts. When a patient presents for a brain MRI to monitor for the presence of ARIA, we must clearly indicate whether ARIA is present and, if so, provide a radiographic severity score. The radiographic severity score provides a score of mild, moderate, or severe for each ARIA-E, ARIA-H microhemorrhages, and ARIA-H superficial siderosis.

ARIA-E is graded based upon the total number of regions of new flare signal abnormality and the greatest linear extent of the largest region. ARIA-H microhemorrhages is graded based upon the cumulative number of treatment-emergent microhemorrhages and ARIA-H superficial siderosis, the number of treatment-emergent continuous regions of siderosis.

Dr. Spampinato: The radiographic severity score is used in conjunction with the severity of clinical symptoms to decide what are the next appropriate steps for patient management. As you can see in the table, in case of mild ARIA-E and mild ARIA-H, in patients that are asymptomatic, it is possible to continue dosing. Of course, that is the case after a discussion with the patient and consideration of risk factors. On the other extreme, we have patients that present with radiographic findings of severe ARIA-E and ARIA-H and patients are present with severe symptoms. In those cases, treatment will be discontinued, and we will need to take care of the patient.

In between these two extremes, there are a set of other patients that have mild and moderate clinical presentation, and mild moderate ARIA severity, ARIA-E and ARIA-H, and also patients that are asymptomatic, but do have findings of moderate ARIA-E and moderate ARIA-H. In those cases, the treatment typically is suspended, and the patient will be monitored clinically, as well as radiographically with serial MRIs. The MRI monitoring will continue to assess, as Dr. Cogswell was saying, to assess the resolution of ARIA-E and the stabilization of ARIA-H. At that point, the clinician can resume discussions with the patient about restarting treatment, of course, after considering the clinical picture and risk factors.

Next, we have an example of ARIA-E and ARIA-H. This is the baseline MRI, and the images shown here are FLAIR images. This is the sequence that we typically use to detect ARIA-E. At baseline, the MRI was normal. The patient underwent their dosing, and after dosing, a follow-up MRI was obtained. The follow-up MRI shows a new area of cortical and subcortical signal abnormality in the parietal region and in the temporal region on the left, and probable sulcal effusion. These are findings highly concerning for ARIA-E. The follow-up MRI showed worsening findings with buildup of more pathogenic edema spreading into the subcortical and deep white matter. As you can see, there is greater, at this point, sulcal effacement with regional mass effect. In light of these findings, we have an area of signal abnormality that is greater than 10 centimeter in extent, this is a case of severe ARIA-E. The follow-up MRI shows complete resolution of the findings. This is something that we observe frequently most of the times with ARIA-E, where the findings are transient and completely resolved.

Dr. Atri: I think you mentioned they may completely resolve, but I think resolved, as you mentioned, with appropriate management. In this case, for example, the ARIA-E one-month postdosing, I guess, was considered severe. Regardless of symptoms, at that point, it would be held. The infusions would be held, correct?

Dr. Spampinato: Yes, absolutely.

Dr. Atri: I think one of the main things is, again, think about ARIA as an imaging abnormality. This tells you nothing about symptoms. That severe ARIA, at this point, we don't know whether it was symptomatic or not in this particular patient. Regardless, based on the protocols and appropriate use, we would hold a treatment here.

Then the first one, the right after postdosing, it seems like, in general, I think if you think about postdosing, one wouldn't be likely to get an MRI right away right after a dose unless it's scheduled. How would you classify that first post-dosing MRI? It sounds like it's one area, but involving multiple, it looks like probably regions or lobes. Maybe I think as far as the AP diameter, I guess, you would look at that and say that that's probably more than five. That's probably moderate, would you say?

Dr. Spampinato: Yes, I believe that this was definitely more than 5 and may have been approaching the 10 centimeter if you look at the greatest dimension, looking at how far it extends into the temporal lobe. That was probably the time when the discussion of stopping occur. The next one was a follow-up MRI to just monitor the radiological findings, but the patient was no longer being treated.

Dr. Atri: That's a good point to make, is that ARIA can evolve even in nature, size, and extent and severity, even while the dosing is being held. That's another, I think, major point for us to think about that, both the radiological follow-up, but also the clinical follow-up that should be close with the patients and care partners.

Dr. Porsteinsson: One thing that I would like to point out is the importance of the reporting. That is the helpfulness when you have a standardized reporting. Because, like you pointed out, Dr. Atri, the first postdose MRI, there are findings there. If this was an asymptomatic individual, and this was read as a mild degree of ARIA-E, as a clinician, I would strongly consider whether to dose through it.

On the other hand, when you hear that it is in possibly two regions, that it is in size that is in the moderate range or nearing the moderate range, that would give me pause. It's extremely helpful for the clinician to have a clear message in terms of the interpretation by the expert, by the neuroradiologist, or the radiologist here.

You see, actually, also something that I often see, and that is that even when you hold dosing, the next MRI may look worse, and then you're truly surprised when a month later there appears to be a full resolution. There are obviously more details here where there are any ARIA-H findings, et cetera, that complicate this, but it is a pretty dynamic series of events.

Dr. Cogswell: I think to follow up on how you were mentioning the importance of categorizing mild versus moderate, I think there's also important nuances of within moderate ARIA-E, for example, there can be a very wide spectrum of degree of involvement. Therefore, the importance for the radiologist is to fully describe the extent of the findings and not just give a label because moderate ARIA-E could be in two regions that are a centimeter, or it could be in three regions that are six centimeters, and much of the brain involved. The importance of the full description of findings like we would in any clinical scenario.

Dr. Atri: That's an excellent point. Yes, I agree.

Dr. Spampinato: For the same patient, we also have the findings on the GRE to review. The GRE image is shown at the bottom. This is the sequence that we use to detect microbleeds and superficial siderosis. At baseline, there were no microbleeds, no superficial siderosis so there was nothing to contraindicate based on the imaging treatment. Next, we have the postdosing MRI where we already reviewed the edema in the parietal and occipital lobe but there are also some subtle areas of dark

signal within the area of edema indicating the appearance of microbleeds. I can see at least a couple on just this image. On the follow-up MRI, the distribution of the edema has increased as we previously know, but now there are multiple new additional microhemorrhages along the cortex and subcortical white matter. It's important in these scenarios to count the total number of new incident microbleeds from the initial treatment dose. Here they were at least 10. That was interpreted and graded as a severe ARIA-H, in addition to severe ARIA-E. You can see on the follow-up MRI, at the top, we have the FLAIR that we reviewed where things have improved significantly. However, on the GRE, we still see numerous microhemorrhages within that distribution. I guess the point is to show that microhemorrhage and superficial siderosis will not resolve. The goal of the imaging monitoring is to make sure that they don't change in number, they remain stable in number and size.

Dr. Atri: In either case, in this particular case, even though the ARIA-E was severe and resolved, and the ARIA-H was severe and stabilized, really hit a threshold of ARIA-H that made it imperative to have a really frank discussion, an open discussion, with the patients and care partners about the fact that the therapy would be stopped because of the severe ARIA-H and really not the E. I think over time we'll understand risks more, but at this point, that really has been the clinical guidance, with the interim ARIA-H being the severe.

Dr. Porsteinsson: I've actually found that in situations where we've stopped treatment, it has often been because of the ARIA-H, because you have either remaining superficial siderosis or the number of microhemorrhages when the ARIA-E has fully resolved. It's just a good reminder that the ARIA-E, which we talk about so much, isn't the beginning or the end. That the ARIA-H matters as well.

Dr. Atri: One of the things I think, Dr. Cogswell, you mentioned is that, while we have ARIA grading schemes that look at the extent, the size, and the nature, then the number of, for example, ARIA-E or ARIA-H, it's really important to think about the components in describing that. Because those are the things that the clinicians are going to need to know to integrate that with other clinical information to guide what they're going to do.

Dr. Cogswell: I think this is rolling out in our practice as well as others. It seems like there could be a lot of confusion around the grading scales, and it seems very complex of, "All right. I need to look at this change from baseline, this change from prior exam, and count. Oh, they were present on baseline, and those don't count. Those microhemorrhages don't count as ARIA." I think if we try and simplify it, that we're looking for change, so we want to know, is there any change from the prior exam, and is there any change since baseline?

I think if people start with that global perspective, that that can be helpful and get them a long way to telling the provider what they need. That is more familiar with how we look at all images of what are the most important reference time points for our comparisons. Then once we decide, yes, no, is there a change, then start teasing apart the individual components to get to an ARIA severity score.

Dr. Porsteinsson: Dr. Cogswell, I think you make a good point about this, but further complicating it is that, just on the reader's end, some of the, for example, microhemorrhages are definite and some are less clear maybe, so they may be reported as possible. How do you handle that? How do you manage that? I'm sure that that's quite a challenge in terms of just keeping an eye on that from one read to another and getting that clearly across.

Dr. Cogswell: Right. I think having clear documentation in the reports and using a template report, which clearly spells out what are the new microhemorrhages or summarizing the microhemorrhages with labels on the images and image numbers is very helpful for reference. The hard part is, what do

the treating providers do with, if you say, "I have two definite microhemorrhages and possibly two new microhemorrhages"? The possible designation leaves ambiguity. That can also occur with ARIA-E.

For example, if a patient is scanned with a different technique or on a different scanner, there may be some differences appearance of how the CSF is nulled in the sulci or in the occipital white matter, leaving ambiguity of, "Is there a change? Is there ARIA-E or not?" We've had a recent case of that and discussed it with the neurologist. “I think there are new findings of ARIA-E, but it's possible that this is due to a difference in technique or some artifact.” With a conservative approach in mind, they're having the patient suspend therapy and come back in a month for a re-pre-brain MRI.

Dr. Porsteinsson: I think that that is an important point. That is that sometimes being cautious and being conservative while this is becoming clear is the better part of valor. That you can pause treatment and restart it four weeks later if the follow-up MRI basically relieves the concerns that you have, that maybe the findings are on the border of where you should stop or pause.

Dr. Atri: That's a great point. I completely agree with it, Dr. Porsteinsson. I think, pardon the pun, it's not always black and white. When we're looking at these microhemorrhages and, gosh, well, is that a microhemorrhage? Is that a vessel? Got a 3T machine with a SWI, very sensitive. You're looking at it on multiple different angles. You're looking at the axial, looking at the coronal, looking at the sagittal, trying to figure out whether this is something new or not. Yes, it isn't quite obvious always.

Other times where patients maybe have gotten imaging at a different facility for whatever reason, and there may not be as good FLAIR suppression or a different machine and a change in technique, which I think, Dr. Cogswell, you were talking about. Some of the subtle things are not clear. Always trying to have that discussion with the patients and families, discussing it with your colleagues, and at times just being humble and saying, "Gosh, well, there's no reason for me to step on the gas here today. Let's hold off on image again and see how things are. Maybe we'll just get a different cut, and it'll become more obvious."

Dr. Spampinato: That's what happens in the radiology reading rooms when there are questionable findings. We often pull other colleagues to review the imaging together. We do the same with our clinical colleagues. Let's review the imaging together. If this is going to make a big difference, and it's important, let's repeat the MRI with the appropriate protocol. If the protocol was not done right. As you said, let's always have the best interest of the patient in mind and post-treatment if there is a controversial finding.

Dr. Atri: What are some other imaging artifacts or things that you find that may cause a little bit of pause and you want to tell our clinicians to think about, whether it's ARIA, ARIA-H or with the ARIA-E? I think I can honestly say that having been doing this for over 20 years, subtle ARIA-E can be difficult. Sometimes in retrospect, you'll look back and say, "Gosh, well, I didn't see that." But it was subtle. It's not an area that's 7 centimeters long. What other things are you finding are potential compounds?

Dr. Spampinato: There are a number of causes. It could be something as simple as motion artifact on the FLAIR image. It is hard to hold still even for a 15-minute exam. When there is motion artifact, our technologists typically try to repeat the sequence to give us good images, but not always that they are successful. That can cause artifactual bright spots in the brain that can be misinterpreted as ARIA or vice versa. We may miss a finding because we think, oh, that's just a motion, and there is something there.

There could be other factors like metal somewhere on the patient's scalp can cause an artifact that looks almost like ARIA-E. Just being on oxygen even can lead to some pseudo-sulcal effusions in the

posterior brain that can mimic ARIA. The other big issue is that of protocol consistency. If we don't use the same protocol with consistency, we may use higher resolution sequence on the baseline study, and then maybe the follow-up study after dosing is the true ARIA protocol that we built. That may lead to difficulties in interpretation. A lot of efforts are going on in the radiology practices to smooth those kinks and have a consistent protocol for this patient population.

Dr. Cogswell: I agree that having a consistent protocol is necessary for accurate ARIA detection really to decrease the potential for some of the mimics or difficulties in comparing two exams. I think another challenge is patients who have existing white matter hyperintensities, especially patchy white matter hyperintensities, that it's hard to detect a new spot, and particularly, like you were saying, the sub-centimeter subtle ARIA-E, which in some cases may have been missed.

You don't see it until retrospect it blossoms into something more, and especially the one little ovoid, a T2 hyperintense focus in the cortex or subcortical white matter that you really need like in a multiple sclerosis exam where you're comparing every white matter dot from two exams. A similar approach is needed here, especially in patients with patchy white matter hyperintensities.

Then, of course, some patients do have progressive white matter disease or a small infarct over the course of their therapy. If we see a new white matter focus, we may call it possible ARIA-E, but if it stays there for several months, at that point, it's probably not ARIA-E. If it looks like another focus of white matter or hyperintensity, that may be what it is.

Dr. Atri: That's excellent for review. One of the things that we do at our centers is we use 3T in the same protocols, but also we do GRE and SWI in order to look at both sensitivity for potentially catching things, but also maybe specificity of whether it was there on GRE or not. Sometimes that helps us delineate the nature of maybe thought as a microhemorrhage, but it's really a vessel or something else, or it's very, very subtle.

I think we've covered a fair bit of the importance of establishing very clear communication and plans and partnering in a patient and patient dyad-centered way, plans regarding any symptoms, what would happen if they go to the emergency department for ARIA, but also the importance of this communication between the ED, the potential vascular, or other neurologists or other clinicians who'll be seeing the patient, and the prescribing clinicians.

Having access to both the information and imaging and aligning those in the right clinical context, making timely decision-making, that potentially is joint because things can be subtle, and a really streamlined interdisciplinary collaboration approach that emphasizes closed loop communication, as well as standardized documentation and reporting. Whereas we talked about ARIA reporting and scales, it's also important to describe the nature of potential changes.

Dr. Porsteinsson: One of the areas that we focused on when we were setting this up commercially, it was, to some degree, easy to do this in the research setting because the infusion center was so well trained. Once you may have to work with more than one infusion center, whom do you ask to check if there are any clinical symptoms of ARIA before they receive the next dose?

We don't get MRIs before each and every dose. That's more so with lecanemab than donanemab. It is critically important to make sure that patients and families are aware that they should report certain common clinical symptoms that are closely associated with ARIA, but also that either the prescriber, or one of the prescriber staff, or, most commonly, one of the infusion nurses goes quickly through a checklist to make sure that there are no symptoms.

Some of these symptoms are common. How do you distinguish whether they are new, whether they are significant? You have to have a relationship with your imaging center to request an urgent MRI at that point.

Dr. Atri: I completely agree. I can tell you, at our center, at least this phased approach we have right now is still very time-intensive and labor-intensive. Before every infusion we have a member of the staff actually call and go through a very systematic checklist for ARIA review of symptoms. That's actually then documented in the EHR. Then we have a difference, and that's within a day or two of the infusion. Then at the infusion center, they have their own checklist, which is a little bit different, but they also go through it and ensure that, for example, medication changes, things like that, are reviewed.

Whenever there's hesitancy about something, it's a really, really important to not ascribe cause to it, but actually communicate it with a team. We try not to put that on the infusion staff. If they gain some information, we don't want to put them in a situation where they're determining whether this is important or relevant or not as much as reporting it to us at that time. We can help make that determination.

What are some resources, I guess, that may be available for ARIA reporting and also for documentation and best practices?

Dr. Cogswell: Here's an example of a reporting template for ARIA. This is available on the American Society of Neuroradiology website as part of their Alzheimer's, ARIA, and dementia work group, as well as listed on the bottom of the reporting template, available through ALZ-NET. This helps the radiologists work through the components of the ARIA severity score. As we had discussed previously, the comparisons with what findings were present on baseline, what findings were present on the prior monitoring exam, if available, and any changes on the current exam.

For ARIA-H to describe or carry forward from prior exams, there were two microhemorrhages present at baseline in the right frontal and left occipital lobe. The prior pre-treatment exam had a new left occipital microhemorrhage. There's no changes on today's exam, so we still have one treatment emergent microhemorrhage or mild ARIA-H. This, I think, is a lot of words perhaps, but at least as people are learning, to help walk them through that process of describing the components of the ARIA severity score, the interval changes, and then correct categorization.

Dr. Spampinato: As we were saying earlier, it's very helpful to annotate the images also on the PACS system and refer to specific image numbers or series so that the next reader will know exactly what you were describing, and it'll be more consistent with your interpretation.

Dr. Porsteinsson: Dr. Spampinato, how important is it for someone like me, a clinician, to be clear about whether there are maybe clinical symptoms or some soft neurological findings that I might be aware of? Is it important for you when you do your read to know about those clinical aspects of the patient's condition?

Dr. Spampinato: Absolutely. The grading scale that we use in radiology is purely based on the MRI. We systematically review the findings and try to grade them into mild, moderate, and severe. The grading scale, per se, is not an actionable scale. We need to really put it in the context of what's the patient presentation. We often encounter patients that come to our outpatient facilities for routine ARIA monitoring, and by the time we see the MRI, we find findings of mild or moderate ARIA, the patients are no longer there for us to really talk to them.

The next step for us is to reach out to our colleague and figure out who is the person that will have the information and can actually find out exactly what is going on clinically so that the next steps can be planned appropriately. As radiologists, we do provide the information, and we need to communicate it, but we need your input, and we need the interdisciplinary collaboration to decide what's next.

Dr. Atri: That was a very, very interesting discussion. We learned a lot about amyloid-related imaging abnormalities, which is a class effect and a potential adverse event of plaque-lowering monoclonal antibodies. We heard about how to classify them, where they may occur, what are important risk factors for ARIA, how to detect them on imaging, what sequences to use, how to document and communicate, and really the importance of having patient-centered shared decision-making with the patient care partner dyad, establishing clear communication channels with them and other colleagues, and really aligning pathways of care so that ARIA could be surveyed, detected, and managed in a timely and appropriate way.

This is a new paradigm of care for all of us. It requires a really system-wide readiness. Learning is in progress. It's something that could be managed in the outpatient setting with patients and families, but it's important to know about. I want to thank both the sponsor and the teams here and my other colleagues for a very interesting discussion. Be well.