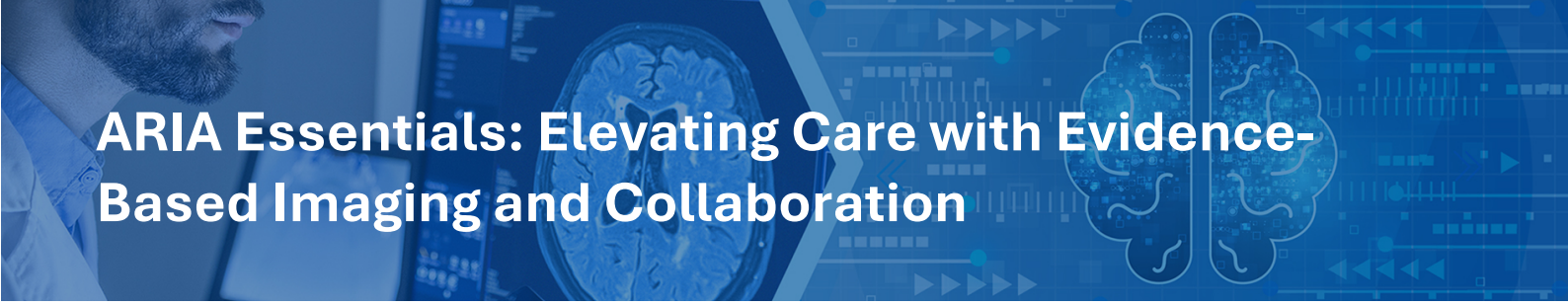

# ARIA Essentials: Elevating Care with Evidence-Based Imaging and Collaboration

## RADIOLOGY PERSPECTIVES

**Petrice M. Cogswell, MD, PhD:** Hello. My name is Petrice Cogswell. I am a neuroradiologist from Mayo Clinic in Rochester, Minnesota. Welcome to our activity, ARIA Essentials: Elevating Care with Evidence-Based Imaging and Collaboration supported by an educational grant from Eli Lilly.

**Maria Vittoria Spampinato, MD:** I'm Vittoria Spampinato. I'm a neuroradiologist from the Medical University in South Carolina.

**Dr. Cogswell:** Here are the learning objectives for our activity. Identify pathophysiologic features that put patients taking anti-amyloid monoclonal antibodies at risk for amyloid-related imaging abnormalities. Apply standard MRI protocols and grading scales to optimize monitoring and detection of ARIA, as well as assessing ARIA severity. Finally, to integrate best practices for interdisciplinary communication to enhance coordination among radiologists, neurologists, and geriatricians in the management of ARIA.

**Dr. Spampinato:** In the next hour or so, we are going to talk about ARIA. In order to better understand the imaging findings, it's important to take a step back and look at the pathophysiology of the disease process. The use of anti-amyloid immunotherapy for Alzheimer's disease is based on the amyloid cascade hypothesis, according to which the buildup of amyloid plaque in the brain triggers a series of events that ultimately lead to neurodegeneration and cognitive decline.

When we start a patient on anti-amyloid treatment, what happens is that the plaque starts to break up and the amyloid that is in the blood vessels, the wall, starts to be mobilized into the perivascular spaces. Normally, perivascular spaces are the pathways through which amyloid is cleared. However, when this system becomes overwhelmed due to an excess of amyloid, the buildup of amyloid and other compounds can lead to neurovascular inflammation with perivascular inflammation, as well as the loss of integrity of the vessel wall resulting in breakdown of the blood-brain barrier with leakage of fluid as well as red blood cells. This phenomenon causes ARIA.

Amyloid-related imaging abnormalities, or ARIA. There are two types of ARIA: ARIA-E, where the E stands for edema and ARIA-H, where the H stands for hemorrhage. They occur in the setting of therapy targeting beta-amyloid, and they can coexist. They both are secondary to leak of either fluid or red blood cells, either into the brain parenchyma or into the subarachnoid space.

How frequently do ARIA-E and ARIA-H occur? They do occur relatively frequently. For example, in ARIA-E, it's been reported that it happens in 15% to 40% of patients with Alzheimer's disease receiving amyloid-targeting therapies. The good news is that most cases of ARIA-E are mild and reversible and asymptomatic. However, there is a minority of cases, less than 7%, that can be severe. Certainly, there are patients presenting also occasionally with symptoms.

On the other hand, ARIA-H does not resolve when the treatment is stopped. Once we are finding ARIA-H, they will persist on the follow-up MRI. We always see some ARIA-H on the follow-up MRI. It's important to keep in mind that ARIA-H happens early during treatment. Most cases are clustered around the first infusions, and then depending on the severity of ARIA, the clinician, in discussion with the radiology and the patient, will decide what's the best next step.

In some cases, with moderate ARIA, clinicians decide to start monitoring the findings with monthly MRI. When findings become either stabilized or resolved, there may be a discussion of restarting treatment again. However, when resuming treatment, it is possible to have a relapse of ARIA, in ARIA-E being described to occur in about 50% of cases.

Let's take a closer look at the ARIA-E on imaging. The E stands for edema and effusion. The key image sequence that we utilize is going to be T2 FLAIR.

There are two possible imaging appearances depending on where the leak of fluid occurs. If there is a leak of fluid into the brain parenchyma, we are going to see the finding of vasogenic edema that we just reviewed. In the cases where the leak occurs through the leptomeninges, instead we're going to have sulcal effusion. Let's take a look at the bottom FLAIR image. As expected, most of the sulci and CSF spaces in this FLAIR images are dark. However, there is a single sulcus in the posterior brain that appears hyper intense. This is a finding of ARIA-E.

It's also important to keep in mind that findings of ARIA-E typically do not have decreased diffusivity, which is helpful to differentiate them from other pathologies such as acute or subacute infarcts. How about location? Typical location, most frequent locations are going to be the occipital and parietal region. However, it can occur in other parts of the brain, including the frontal lobe and the posterior fossa. ARIA-E is transitory, so it does resolve within a few weeks. Sometimes it takes a little longer.

As we discussed, the H in ARIA-H stands for hemorrhage. In order to detect it, we need sequences that are sensitive to blood products. The key sequence that was widely used in the clinical trials that led to the approval of these drugs is the GRE, so that's certainly a key sequence. In addition, an optional SWI can be added. As far as the imaging appearance, when there is the leak of blood products into the brain parenchyma, the finding of ARIA-H consists of microhemorrhages as shown in the image at the top. You can see how there are clusters of little hypointense foci consisting with microhemorrhages.

On the other hand, when the leakage of blood products occurs along the leptomeninges, so the finding is that of superficial sclerosis as shown in the case at the bottom, where there is a curvilinear hypointensity along the brain surface.

Different individuals have different risk of ARIA. There are some risk factors that can be identified with MRI, but there are also some clinical risk factors. Among the clinical risk factors, a major one is being a carrier of the *APOE4* allele. That's why clinicians test for this gene before starting treatment, and this is important in the discussion of risk and benefit for treatment decision-making. As far as other genetic risk factors, there are certainly other genes that are involved in overproduction of amyloid beta in regulating the clearance of amyloid, and neuroinflammation, and these are also other potential risk factors under investigation.

In addition to *APOE4*, another important risk factor is that one detected on MRI. That's why it's so important to obtain before starting treatment, a baseline MRI to review the presence of any pathology, and that is the presence of multiple cerebral microhemorrhages. I believe that we're going to talk about this more in detail later. Other risk factors for ARIA-H include age, the use of antithrombotic medication, and prior strokes.

There are other disease processes that are very similar in appearance to ARIA. First and foremost, the cerebral amyloid angiopathy-related inflammation, or CAA-RI. This disease process is characterized by spontaneous sulcal effusions, as well as mesogenic edema, and microhemorrhages, as well as superficial sclerosis, so all the major findings that we see in ARIA. Another disease process that is

similar is posterior reversible encephalopathy syndrome, also presenting with multiple areas, usually of mesogenic edema, as well as microbleeds, subarachnoid hemorrhage, and sometimes even intraparenchymal hematomas.

How can we differentiate these other entities from ARIA? The first important thing to consider is find out if the patient is indeed on monoclonal antibodies to remove amyloid plaque. Let's look carefully at the medical record. If we don't have the information because maybe the patient comes from an outside hospital, let's try to find out more about the patient by reaching out to the ordering physician. In addition, clinical presentation will be certainly different with some of these entities. For example, CAA-RI, in my experience, it's usually symptomatic. Patients present with neurological deficit, which is not always the case with ARIA and PRES certainly has clinical triggers that are very specific, such as hypertension, immunosuppression, and so on.

We just went over the basic mechanisms of ARIA-E and ARIA-H. Dr. Cogswell, what do you think are the most important factor that you take into account as you read these cases in your practice? For example, I just realized that we have the *APOE4* available in the medical record for every patient. I was not aware of this, so that was a learning point for me.

**Dr. Cogswell:** As you discussed, underlying cerebral amyloid angiopathy is a major one of the primary risk factors for ARIA and ties into the underlying pathophysiology. You've discussed related to amyloid removal from both the parenchyma as well as the blood vessels, potential overloading of the perivascular drainage pathways, and worsening of cerebral amyloid angiopathy as a part of the pathophysiology of ARIA. In terms of us as radiologists, identifying those findings of cerebral amyloid angiopathy prior to treatment are very important.

**Dr. Spampinato:** Any other comments about how to differentiate ARIA from lookalike conditions? Certainly, the clinical presentation comes to mind, and finding out more about any treatment patient is on.

**Dr. Cogswell:** I agree that, as you mentioned, even before considering the imaging findings is looking into the patient history. I think then the first branch point in that differential diagnosis is, is the patient receiving anti-amyloid immunotherapy. If yes, then we put ARIA on top of our differential diagnosis. Once, then when we're going down to the imaging findings. I think looking at the diffusion weighted imaging is the next branch point as if we see a region of new edema. Often, these patients may present with a focal neurologic deficit when ARIA is symptomatic. Then, differentiating ARIA from acute ischemia is very important. ARIA, which would not restrict diffusion, and an acute infarct which would. The patient history of anti-amyloid immunotherapy and then, right, the imaging findings including whether there's diffusion restriction.

**Dr. Spampinato:** Is it sometimes a challenge when a patient come through the ED because they have symptoms? Most likely, the indication is going to be rule out stroke. I had a similar case recently, and then when looking into the chart more carefully, it became apparent that the patient was indeed on anti-amyloid immunotherapy. That's a challenge that I encounter quite frequently.

**Dr. Cogswell:** Yes. That's one of the main situations in which there have been poor outcomes in these patients in which they present to an emergency department and are thought to be having an acute infarct and receive thrombolytic therapy when in fact, it was ARIA and with then progressive hemorrhage and edema once receiving that therapy. The importance of brain MRI early in these patients who are on therapy and presenting with new neurologic symptoms is very important.

**Dr. Spampinato:** The takeaway message is to really know the patient's history and review the chart carefully, as important information should not be missed.

**Dr. Cogswell:** Next, we'll discuss the role of imaging in both selecting patients who are appropriate for therapy, as well as monitoring for the adverse event of ARIA during the course of therapy. We'll discuss the exclusionary findings as have been laid out based upon what was done in clinical trials, as well as appropriate use recommendations that have been provided for implementation in clinical practice.

The first of these exclusionary criteria are findings of cerebral amyloid angiopathy, as we discussed, due to the fact that these are risk factors for the adverse event of ARIA. Specifically, greater than four micro hemorrhages, presence of superficial siderosis, or any low bar macro hemorrhage are considered exclusionary for treatment.

In addition to the chronic findings of cerebral amyloid angiopathy, findings of cerebral amyloid-related inflammation are exclusionary. As we see in this patient, this occurs in the form of edema or a sulcal effusion with chronic findings of microhemorrhages or siderosis. In this patient, they had left frontal edema, left parietal edema, and sulcal effusion, which was found when they presented with new seizures and headaches. Follow-up imaging demonstrates resolution of these findings, and again, findings very similar to ARIA, but this patient was not receiving anti-amyloid immunotherapy, These findings occurred spontaneously.

Additional findings on brain MRI that would exclude a patient from anti-amyloid immunotherapy are the presence of chronic ischemic changes, specifically greater than two lacunar infarcts or the presence of the large cortical infarct.

Additionally, advanced white matter hyperintensities as defined as a Fazekas score of three are exclusionary.

Additional findings have excluded patients from clinical trials of anti-amyloid therapies such as vascular malformations or cavernous malformation, the presence of a brain aneurysm, or masses such as a meningioma. However, some of these findings are not considered necessary exclusionary for treatment and clinical practice is laid out in appropriate use criteria. Treatment of these patients should be considered based on the clinical context and, for example, if this finding may require future intervention.

The brain MRI findings are just one component of evaluating a patient's appropriateness for therapy. The therapy decision-making process will also consider the disease stage, biomarker characteristics, *APOE4* carriership as we discussed, another risk factor for ARIA, as well as chronic conditions that may require the use of anticoagulants or present the need for thrombolytic therapy. These findings, as well as clinical background and history, will be used to have an informed discussion with the patient about the risk-benefit of the therapy and the patient's willingness and desire to move on with therapy as well as the clinician's recommendation for appropriateness.

Now we will move on to reporting of these imaging findings and how we may clearly communicate them to the referring providers. We'll discuss the communication of findings both on what we'll call a pre-treatment brain MRI designated as an AD therapy enrollment exam, as well as what we'll call AD therapy monitoring exam, so monitoring for ARIA during the course of therapy.

Important imaging findings to convey on the pre-treatment evaluation are those that are included as exclusionary in the appropriate use criteria. We must lay out the discrete number of

microhemorrhages present on the pre-treatment brain MRI, the number of regions, if any, of superficial siderosis, extent of white matter hyperintensities, which may be described as mild, moderate, or severe, or via Fazekas grade, and describe the presence of any infarcts.

On MRI exams done for patients on therapy to monitor for ARIA, we must describe findings in order to reach a radiographic ARIA severity score. A radiographic ARIA severity score of mild, moderate, or severe should be given for each ARIA-E, ARIA-H microhemorrhages, and ARIA-H superficial siderosis. ARIA-E radiographic severity score is based on the number and size of regions of new FLAIR hyperintensity. The regions of FLAIR hyperintensity are measured to include both any new parenchymal edema, sulcal effusion, as well as mass effect gyral swelling.

One region of new FLAIR hyperintensity, less than 5 centimeters, is mild. More than one region, each less than 10 centimeters in greatest linear dimension is moderate ARIA-E. Severe is any new FLAIR signal abnormality measuring greater than 10 centimeters. ARIA-H microhemorrhages is graded based upon the cumulative number of treatment emergent microhemorrhages, 4 or less being mild, 5 to 9, moderate, and 10 or more new microhemorrhages severe ARIA-H. ARIA-H superficial siderosis is separately graded from ARIA-H microhemorrhages and is based upon the number of treatment emergent regions of superficial siderosis with one being mild, two being moderate, and three or more severe.

We need your thoughts on the degree to which that's been able to capture the variability we see between patients or over serial exams in a patient?

**Dr. Spampinato:** Yes, absolutely. The grading scale is great because it provides a framework for us to organize our imaging findings and to provide actionable findings for the clinicians. Obviously, it cannot be used as a standalone tool because it does not take into account the patient presentations and their symptoms. That's why it's so important for us to interface with the referring clinicians and neurology and other specialists so that we can integrate our side of things, use our imaging expertise to guide their clinical judgment.

I have to say that there are some cases, especially when more complex cases with multiple relapses, where it gets a little tricky to fit the information in the standardized grading scale. Otherwise, it's been very helpful, also a great teaching tool for the residents and fellows.

**Dr. Cogswell:** Yes, I agree that in terms of providing a structure and framework on which to categorize findings, it's really helpful for us in implementing ARIA monitoring clinically. I think one of the challenging aspects is then from that conveying change to referring providers. I think part of it they want to know are the patient's imaging findings getting better or worse? It's still important in our findings to include the description of what is happening in comparison with the prior exam and that someone with mild or moderate ARIA may have quite a bit of improvement in their imaging findings but maybe not change categories.

I think that is where it's important maybe to put more words, maybe in our impression than “moderate ARIA,” but adding “moderate ARIA, improved from the exam one month ago or progressed” to make sure to also provide that degree of change to the referring providers.

**Dr. Spampinato:** Basically, in addition to, basically, the checklist and the standardized wording, it's very important to have a free text paragraph almost with all the other thoughts that are important, right?

**Dr. Cogswell:** This radiographic ARIA severity score is used along with any patient's symptoms to determine the patient's eligibility for continued drug dosing. Ideally, on these monitoring MRI exams, the patient has no symptoms and no ARIA, and they continue with their regularly scheduled dosing. However, if there is any radiographic ARIA or any clinical symptoms, the therapy may need to be suspended or permanently discontinued. Based upon what was done in clinical trials and provided in appropriate use criteria, the dosing should be suspended for any moderate ARIA or the presence of any clinical symptoms and dosing permanently discontinued if there is severe ARIA or experience of severe clinical symptoms.

If a patient's dosing is suspended for mild or moderate ARIA with or without symptoms, monthly brain MRIs should be performed to evaluate for the resolution of ARIA-E and stabilization of ARIA-H, at which time clinical judgment may be used to determine appropriateness for continued dosing. While we've been provided appropriate use recommendations for how to manage ARIA, you maybe notice that institutions or practices may take perhaps even more conservative approaches.

For example, even with an asymptomatic patient and mild ARIA-E, our neurologists have chosen to pause dosing in those patients and perform monthly brain MRIs to evaluate for the resolution of ARIA-E. At that point, once ARIA-E has resolved and there's no new findings, then proceed with resuming therapy. Dr. Spampinato, how has your practice been implementing these appropriate use criteria?

**Dr. Spampinato:** At our institution, in patients that are asymptomatic and have mild ARIA, our neurologists thus far have continued with dosing, and they may have done dose adjustment, I'm not sure, but they have continued. As far as the more severe cases, we were lucky so far not to experience that scenario in our practice.

**Dr. Cogswell:** That's great. I think another consideration which may be brought up about moderate ARIA is regions less than 10 centimeters, but in some cases, may be very extensive if the patient has multiple regions of brain involvement of ARIA-E. That although each is less than 10 centimeters, could involve many parts of both cerebral hemispheres. I think that is another consideration in terms of looking at the global extent of involvement and deciding whether to resume therapy in a patient.

**Dr. Spampinato:** In those cases, we have been monitoring with monthly MRI and reviewed the multiple studies longitudinally. Until we are pretty confident that all the findings have resolved and stabilized, there is just monitoring.

**Dr. Cogswell:** Similarly, we monitor those patients. I think even after that ARIA-E resolved, if it was quite extensive, in some cases, the provider may be hesitant to restart that patient on therapy, even though it was technically moderate but very extensive. These are interesting nuances, I think, that come up in the real-world clinical implementation.

Now that we've discussed some of the important brain MRI findings, we're going to review how to perform the MR imaging for patients on AD therapy. We'll discuss this again in terms of protocols specific to AD therapy enrollment. That is again the pretreatment evaluation versus AD therapy and monitoring the exams to monitor for ARIA in a patient on therapy. In both of these protocols for both enrollment and monitoring, there are three key sequences that should be performed in all exams in a consistent fashion. Those are a GRE or SWI, a T2 FLAIR, and diffusion-weighted imaging.

Additional sequences may include a 3D T1 and a T2. Particularly for an enrollment exam, we would expect all five of these sequences to be included as the enrollment exam may often coincide with the dementia evaluation. These sequences would be the same as that would be performed as an MR brain without for dementia assessment.

Dr. Spampinato, how is your practicing managing patients who may have these findings on their pretreatment brain MRI?

**Dr. Spampinato:** Our approach is conservative in patients with vascular malformation such as cavernous malformation, aneurysms. We, initially, did not consider eligible for treatment patients with meningiomas that were more than 1 centimeter, but we are more and more including patients with small incidental findings like that.

**Dr. Cogswell:** Next, we'll review some of the specifics of the imaging to be performed. First of all, field strength. It is recommended that imaging is ideally performed at a field strength of 3 tesla and a minimum field strength of 1.5 tesla, and that imaging be performed on a consistent scanner and field strength over serial exams in a patient. In regards to details of the three key sequences. First, the T2 FLAIR is performed for ARIA-E detection and may be done using either a 2D or a 3D technique, whichever can be done consistently in your practice with high quality. For ARIA-H detection, a GRE is what was performed in clinical trials and on which the ARIA severity scoring system was based. However, SWI is more sensitive for the detection of blood products. Many practices have desired to be as sensitive as possible for detection of any pre-existing microhemorrhages or any that may occur with therapy and have chosen to implement SWI either along with GRE or in place of it.

It should be noted that in those circumstances, more microhemorrhages may be identified on SWI versus GRE and, therefore, may lead to a more conservative treatment approach. The third key sequence is diffusion-weighted imaging, which will help differentiate ARIA-E from acute ischemia and can be performed according to standard clinical protocols.

Dr. Spampinato, has your practice developed separate imaging protocols for AD therapy enrollment and monitoring or just perhaps an overall AD therapy imaging protocol?

**Dr. Spampinato:** Yes, absolutely. Our AD therapy enrollment patient is the same as our general dementia patient protocol, while we have implemented the shorter AD therapy monitoring. Initially, the FLAIR sequences were not the same in the dementia protocol and AD therapy. We had a 3D FLAIR, and in the AD therapy monitoring, we had a 2D FLAIR, but we decided to adopt the 3D FLAIR across the board to have the same comparison of findings.

**Dr. Cogswell:** That's a great point to highlight the importance of consistency over serial exams, that things like changing between MR scan vendors can change the appearance of the white matter as similarly, I think changing between a 3D and 2D FLAIR can change some of the appearance of the white matter regions, particularly sometimes that occipital white matter where ARIA is most common and potentially lead to ARIA mimics due to change in technique. That's a great point to highlight the need for consistency between the enrollment and monitoring exams.

Here's an example to demonstrate the importance of using a consistent set of sequences, consistent imaging parameters across serial exams in a patient. This is a patient who has both ARIA-E and ARIA-H. On the first dose post-dosing exam shown on the left, we see that there are several microhemorrhages. On their follow-up exam the next month, SWI was performed in place of GRE, and we see that there are several new microhemorrhages. However, it is unclear whether these are, in fact, new or if they are just better seen due to differences in technique.

Once again, important to choose a consistent approach to use across all serial exams in a patient. FLAIR, the GRE, and DWI are the three key sequences in our AD protocols, and as I had discussed, there are potential benefits of using an SWI, a more sensitive sequence for the detection of ARIA-H.

Are there trade-offs between using GRE and SWI, and what considerations have there been in your practice?

**Dr. Spampinato:** Yes. Traditionally in our practice, SWI was the go-to sequence for this purpose in adult protocols. When we started seeing this patient in September of 2023, we initially didn't change that. Then we started seeing that patients were coming in with outside MRI from other institutions that serve as their baseline MRI, and that included GRE sometimes as opposed to SWI. We thought it would be wise to include the GRE so that we could have a sequence that is more comparable for these outside studies. Certainly, GRE has advantages as it can be more easily standardized, it's more widely available. We're very used to SWI, so we do have that still in our protocol. What is your experience?

**Dr. Cogswell:** We have been using both the GRE and SWI. While the SWI is more sensitive. I think there's also the potential for more false positives. There may be some cases where the improved resolution of the SWI can help us differentiate a microhemorrhage from a vessel. There's other times though where we just see so much more on the SWI that a vessel may, on the other hand, mimic a microhemorrhage more frequently than on the GRE. The SWIs and the other trade-off is they take longer to interpret than a GRE. Right now, we've been using both and there's been times where having both is helpful for troubleshooting and determining what we think is a real microhemorrhage versus not.

**Dr. Spampinato:** I have similar experiences with wondering about findings, whether they are microbleeds or vessels. Sometimes subtle changes from one SWI to the other. Do you have any tips for those that use both sequences, what do you report in your standardized report?

**Dr. Cogswell:** That's a great question. Based upon these discussions and advice from the American Society of Neuroradiology, Alzheimer's Association, the Alzheimer's ARIA and Dementia Work Group of the ASNR, we have reported what we think is the true number of microhemorrhages using all the information we have. I think that can be confusing. That is what we've said in our practice to look at both.

There's times in a report someone would say I see this many on the SWI and this many on the GRE, and I think in a subspecialty practice where they can handle that type of nuance, I think that's fine. I think oftentimes an interpretation that included two sets of counts would be very confusing for referring providers. Hence, if you have both, we have to report what we see on the SWI if it's performed. The easiest thing is to use both to troubleshoot and say this is how many microhemorrhages I think are real and present to report that.

**Dr. Spampinato:** I agree with that. I wanted to add that our societies have done a lot of work with the vendors to standardize the sequences, right? When it was time for us to introduce a GRE, we actually went on the ASNR website and downloaded the specific one for our vendor and our scanners, which was amazing.

**Dr. Cogswell:** As I have discussed, it may be helpful to have separate imaging protocols for the AD therapy enrollment exams and the monitoring exams. This may be helpful in a couple of ways. The first is that if you, in your practice, desire to have different protocols for each of these. For example, the AD therapy enrollment to mirror that of a full dementia exam, whereas the AD therapy monitoring, some practices have chosen to make that an abbreviated protocol to help accommodate increased scan volumes.

Another way in which the differential naming process for these protocols may be helpful is in your clinical workflows, and that there may be discrete orderables linked to each of these, which will then also be associated with individual imaging protocols as well as reporting templates. In those workflows and these naming practices, it'll help make the radiologist aware of what they should be reporting in an exam. Specifically, do I need to report the findings in order to evaluate treatment eligibility, or do I specifically need to be looking for and reporting any findings of ARIA?

We've discussed multiple brain MRIs to be performed over the course of the treatment with anti-amyloid immunotherapy. The specific timing of these brain MRIs has been laid out both in appropriate use criteria and the FDA labels, and there are separate schedules for each agent. Both of these MRI schedules for donanemab and lecanemab specify a brain MRI prior to the initiation of therapy and appropriate use recommendations specify that this MRI should be done within a year prior to therapy.

There are then, as we see here, multiple brain MRIs during the first year of therapy to evaluate for asymptomatic ARIA. Additional brain MRIs may be required in two circumstances. First, if ARIA is identified, monthly brain MRIs are required to evaluate for the resolution of ARIA-E and until the stabilization of ARIA-H. The second scenario, as we discussed, is if a patient presents with clinical symptoms that may be related to ARIA, additional brain MRI is warranted.

Now we'll go through some examples of ARIA. First, this is a patient on anti-amyloid immunotherapy, and we have three selected slices from the baseline FLAIR exam showing minimal white matter hyperintensities. On the first postdosing exam, we see a new T2 hyperintense signal in the cortex and subcortical white matter involving the temporal, parietal, and occipital lobes. Due to the extent of this ARIA, the patient's dosing was held, and repeat imaging was done a month later. We see that despite the suspension of dosing, the ARIA has progressed. There is now extensive edema and mild associated mass effect involving that left temporal, parietal, and occipital lobe. Two months later, we see that the ARIA has resolved in keeping with the transient nature of ARIA. This is an example of severe ARIA-E, so is a single region, but measuring greater than 10 centimeters in greatest linear extent.

This patient also had findings of ARIA-H, so we're showing single slices here from the baseline T2 FLAIR and GRE. Again, minimal white matter hyperintensities and no pre-treatment microhemorrhages. On the post dosing exam on which ARIA-E was first recognized, we see that there are few new micro hemorrhages. On the next post-dosing exam, there was progression of both the ARIA-E as well as ARIA-H with several new microhemorrhages. Then, as is often the course when there's co-existent ARIA-E and ARIA-H at the time point where the ARIA-E resolves, we may continue to see more microhemorrhages as those heme products coalesce and become more visible on MRI. This was an example of severe ARIA-H micro hemorrhages that occurred along with ARIA-E.

**Dr. Spampinato:** This is the next case. The baseline MRI was basically normal. These are two selected FLAIR images from that MRI. The patient was deemed eligible for treatment, and after dosing on the first MRI after the infusion, you can appreciate multiple areas of subcortical increased T2 signal in the right temporal, right occipital lobe, as well as in the left cerebellar white matter. Since we have multiple locations of ARIA-E and there are less than 10 centimeters this case was interpreted moderate ARIA-E. Due to these findings, the treatment was suspended, and the patient underwent Serial MRIs for monitoring every month. On the next MRI, you can see where the white arrowhead is, that there is a new area of subcortical edema that appeared. The other findings are stable or improving. Then, on the follow-up MRI, there is resolution of findings. The brain looks normal.

These are two SWI images from a baseline MRI where we didn't see any microbleeds or superficial siderosis. The patient was deemed eligible for treatment. However, on the post-dosing MRI, you can

see how in the bilateral cerebral wound, there are linear areas of hyperintensity consistent with superficial siderosis. The SWI also, upon careful review of contiuous images, we found a new left frontal microbleed. At this point, the patient started being monitored with monthly MRI after treatment was suspended and you can see how findings remained unchanged. Again, superficial siderosis of the cerebellum and left frontal microbleed. After several months of monitoring with stable findings after discussion with the patient, the risks and benefits of treatment was resumed. Sometimes, of course, there was a new FLAIR of ARIA-E that occurred in November with a new area of superficial siderosis in the left frontal lobe.

This was a patient that had a normal brain MRI with the exception of mild white matter disease, and patient was referred for treatment. On the follow-up MRI after dosing, we were informed by the referring physician that the patient had a recent head trauma, which was extremely helpful. Here are the MRI images. On the FLAIR image at the top, you can see how there is some hyperintensity in the left frontal subdural space. This finding was interpreted as a subdural hematoma secondary to the trauma. Then on the SWI, we noticed multiple microbleeds, a total of five. That would make the case a moderate ARIA-H. At that point, we got in touch with the referring neurologist to discuss the case and to learn more about the mechanism of trauma. It sounded like the trauma was a minor trauma, a fall from standing. We conveyed the results of subdural hematoma as well as moderate ARIA-H. Dosing was suspended and there was a plan for short interval follow-up with MRI.

The next case was a patient that on baseline MRI had mild to moderate white matter hyperintensity. The patient was eligible for treatment and underwent their first dose. The MRI after infusion demonstrates two new areas of signal abnormality in the brain parenchyma, a right occipital subcortical hyperintensity. In the left frontal lobe, we noticed that in an area where there were findings of white matter hyperintensity, the changes were now more extensive with involvement of the subcortical white matter. Based on the findings of edema and signal change in two areas of the brain, we graded this case as a moderate ARIA-E and we discussed the case with our referring clinician. It was decided to suspend treatment and the patient underwent monthly monitoring MRI to assess further these findings. On the subsequent MRI, the findings were less conspicuous and finally completely resolved.

**Dr. Cogswell:** I think this is a great example to highlight the importance of catching, I would say in this case it was moderate, but the importance of catching small areas of ARIA-E or in this case multiple and intervening with stopping dosing before this potentially progress to more extensive ARIA. I think the other point this case very nicely highlights is how ARIA-E may be challenging to identify in patients who have patchy white matter hyperintensity like this.

That region on the left, as I said, many people may gloss over that as just part of their chronic white matter disease. This is a very nice example to highlight the importance of comparing with that baseline exam and particularly, with patients with this patchy white matter hyperintensities.

**Dr. Spampinato:** I wanted to add that 3D FLAIR seems to me particularly helpful with some more refined assessment of white matter hyperintensity. We already had in our dementia protocol, but we adopted also in the ARIA monitoring protocol.

These images are close-up images of the previous case. I wanted to look more in detail at the right occipital lesion where we have two findings of ARIA-E, two examples. The blue arrow indicates an area of subcortical edema, but more posteriorly, the yellow arrow indicates sulcal effusions.

A patient had only mild white matter hyperintensity at baseline. The patient underwent their first infusion and on the follow-up examination, new findings were identified. There are new areas of T2

hyperintensity, one near the right occipital horn, and one in the region of the cortex internal capsule. These two areas are both less than 10 centimeters. With two new areas of signal abnormality in a patient that is on anti-amyloid immunotherapy, the concern is that of moderate ARIA-E. We were somewhat puzzled by the right cortex nucleus lesion because we had not encountered a similar lesion, so we thought it was somewhat atypical. We reached out to the provider to discuss the case. After discussing with the neurologist, we thought that certainly it would be appropriate to closely monitor this finding and we made sure to schedule a follow-up MRI, which was performed and revealed the resolution of the findings. I guess I learned something new that you can have findings of ARIA also in the basal ganglia region.

**Dr. Cogswell:** I think that's a great case to highlight if you see unexpected findings to consider something other than ARIA as we may be. We're working on training people to know what ARIA is and recognize it, but at the same point, we need to approach these exams like any other and that not just expect everything we see to be ARIA and that if there is an unexpected finding or questionable ARIA to continue to follow that exam. In some cases, patients, if that did not resolve, maybe they would go on to have a brain MRI with contrast if we start considering something else.

**Dr. Spampinato:** Absolutely, that crossed our minds and we certainly would have done that had the finding not improved. That was an interesting case. Here is a more mild case of ARIA. The baseline MRI shows a couple of microhemorrhages in the left temporal region, right temporal-occipital region. This was the baseline exam. Since the number of microhemorrhage was less than five, the patient was considered eligible for inclusion and underwent dosing. On the post-dosing MRI, we found a new microbleed indicated by the yellow arrow. That would be a case of mild ARIA-H. Dosing was continued in this case, but the patient was closely followed with imaging.

We talked about pathologies that can mimic ARIA. This is the case of a 65-year-old woman with rapid memory decline. She underwent an MRI, and the FLAIR image is shown on the left. You can see how there is an area of so-called hyperintensity. On the SWI, there are numerous micro hemorrhages, certainly more than 10. These are findings that we normally expect to see in patients with ARIA, but this patient was not on anti-amyloid drugs. We have to think about other options. The working hypothesis for this case was that of cerebral amyloid angiopathy and possibly cerebral amyloid angiopathy-related inflammation because of the effusion.

**Dr. Cogswell:** Some institutions may not have the ability to have dedicated imaging protocols for ARIA or the ability to implement them. What has been your experience with that?

**Dr. Spampinato:** Although my institution is a mid-sized academic institution, it's been a challenge as we work with many, many scanners. New scanners are added. Other scanners undergo software upgrades. What's been helpful for us is when the department has identified a lead MRI tech that is actually in charge of the protocols, and that's what she does most of the time. Having that person coordinating the protocol has been amazing. Despite that, we are struggling to develop the appropriate orders. It takes a long time.

**Dr. Cogswell:** We've had the ability to integrate separate AD therapy enrollment and AD therapy monitoring protocols and templates into our clinical workflows, but we know that may not be the reality for a lot of practices. I think it's important to highlight that the three key sequences for ARIA monitoring are part of our brain without protocols, and so standard T2 FLAIR and DWI work. I think the most important sequence of those to make sure is being performed with high quality is the gradient echo.

The GRE in order to be fast in some implementations may not have the correct parameters for optimal detection of blood products. I think if that sequence in particular, is checked to have appropriate echo times and slice thickness per the recommendations for ARIA imaging, and if that is implemented in their brain without protocols, then that is something that could be used more generally also for ARIA detection.

**Dr. Spampinato:** That's a great tip to really implementing more widely so that we can capture also those patients that come in for stroke or other indications so that they are scanned with appropriate GRE.

It is very important to establish interdisciplinary collaboration with our clinicians. Certainly, a first step is to establish channels of communication that are approved and compliant. For example, we use in our practice the Seqster chart in our electronic medical record as well as Microsoft Teams is another option for interdisciplinary teams.

Depending on the setting just a traditional phone call or paging system is appropriate. What is very important is to establish upfront within your practice what type of communication will take place depending on the findings that you encounter. In other words, if interpreting a baseline MRI, this is not an emergent case, most likely that finding can be conveyed just through the standard reporting. However, in the presence of findings of mild, moderate, severe ARIA it's important to engage the clinicians. I would be interested to know what type of communication methods do you use for those scenarios.

**Dr. Cogswell:** For our clinical communications they're similar to you. There are the methods through the electronic medical record system that allow us to communicate findings to providers and can be marked as just needing follow up urgent or emergent findings. That is one of the encouraged ways throughout the institution to communicate findings. Similarly has been applied to the ARIA monitoring, again, to convey findings of when radiographic ARIA is present.

I think though a lot of people also in some cases prefer to have a phone call, and that can be very helpful especially in cases where it may be unclear what the clinical context is to have that discussion with the referring provider and help potentially clarify the overall picture.

**Dr. Spampinato:** Absolutely. Also, because the clinicians do have questions and as we were saying, not everything fits in the grading scale so there are other information that they want to discuss with us before deciding the next steps. It's very important to read the studies in the appropriate clinical context. It's important to have up-to-date information about patient symptoms. We don't always have that, but it would be ideal to know what's going on.

It is important to have not only the imaging report, but also the appropriate clinical information in a centralized place, in the medical record so that everybody's on the same page with what is going on with the patient, what is the current plan for treatment.

**Dr. Cogswell:** As we've discussed through the reporting and communication of these findings of ARIA that there's specific components that we need to include and the use of a templated report may help to communicate those clearly to the referring providers. This is an example of a reporting template to assess for ARIA that provides the components needed to arrive at each ARIA-E, ARIA-H microhemorrhage and ARIA-H superficial siderosis severity score.

These include noting for ARIA-E on the prior exam, did they have any ARIA? Is there any new ARIA on today's exam? We want the total current regions of FLAIR signal abnormality and their size to

determine an ARIA-E severity. I'll note that for each of these, it requires comparison to the most recent prior AD therapy monitoring exam if present as well as that enrollment or pre-treatment baseline exam in order to note, so what was there at baseline? Is that not included in ARIA, if there were baseline microhemorrhages, for example, but we want to know what is new since starting therapy. I think in some ways, there may be a lot of words here to work through in this template. In addition to communicating findings to providers, it can serve as an aid to the radiologist to work through what are the findings I need to document and how do I arrive at an ARIA severity score.

**Dr. Spampinato:** I wanted to add that there are templates developed by the ASNR, specific for a baseline pre-treatment MRI read as well as ARIA monitoring that can be easily downloaded and installed on your dictation system.

**Dr. Cogswell:** The structural reporting templates can help standardize ARIA communication. Do you find though that they're too rigid or don't include the specific information that you need to in communicating the findings?

**Dr. Spampinato:** Well, just like we discussed before, sometimes it's hard to fit all the nuance of a case especially when we are comparing a study with an outside study that is performed in a different institution. Maybe a study was done on a 1.5 tesla MRI, another 3 tesla, so there is a lot of nuanced information that needs to be expressed, so that is one of the challenges.

**Dr. Cogswell:** I feel like any other templated report, it's there to serve as a guideline for reporting a specific finding on the brain MRI but that we need to remember, so that we're looking at the whole brain MRI in the clinical context and so that should include any other findings and not just our documentation of ARIA.

Also that while we want to know the specific number of microhemorrhages, that description of ARIA-E extent regions of involvement and change from a prior exam are very important and so those aspects should also be included.

In terms of interdisciplinary collaboration in ARIA management, what have you found to be the biggest barriers to timely discussion with the referring providers?

**Dr. Spampinato:** An issue is, of course, getting ahold of the right person at the right time as not everybody works the same schedule. For a lot of cases, we use the electronic medical records, Seqster, for example, the milder cases. We try to leave a message also with another provider in the same group as possible. Sometimes since we are in an academic institution, when we cannot get ahold of the provider, we page the neurology resident on call and they help us out, track down the person that knows the patient and can help us out. What have you experienced in your practice?

**Dr. Cogswell:** I think one of the challenges is that the AD therapy treatment teams may involve many people from different specialties which is an excellent advantage to have these teams. On the same hand, when it comes time to, let's say checking clinical symptoms and radiologic findings prior to the infusion, we want to make sure that the right people get the information.

I think integrated ways within the electronic medical record to make sure that the communication are going to all the people who need to have it is one way that may help us streamline that type of communication.

Finally, when dealing with moderate to severe ARIA, radiologists play a critical role as we've discussed in communicating the findings. How proactive do you think radiologists should be in terms

of not just reporting the imaging findings but also conveying the implications for therapy according to appropriate use recommendations?

**Dr. Spampinato:** Absolutely. As the radiologist, we are the imaging expert. Our role is to identify the finding, dealing with the complexity of the imaging with all the issues that we discussed of like sometimes lack of consistency and come up with the best grading of ARIA that we can reach out to the providers and discuss the findings. It is not really our role to decide management, but to serve as a consultant to support the decision-making process of the provider. That's my take on this.

**Dr. Cogswell:** I agree. I think if there's questions here. Let's see. In terms of who is your audience and what is their referring provider, what is their knowledge of ARIA? That perhaps maybe if you're not sure the referring provider is as familiar with the process, maybe that's a time where a phone call would be helpful to say, "I think this patient is on anti-amyloid immunotherapy. What I'm seeing here is I think moderate to severe ARIA." That would, at least, open up the opportunity for questions in further discussion.

Whereas I think within our own clinical practice, I know the subspecialty neurologists who are referring patients are very on top of the findings and management. That extra level of discussion would not be needed.

**Dr. Spampinato:** Let's go back to the initial cases for further discussion of the imaging findings.

In this case, the most important piece of information that we need to know is whether the patient is on anti-amyloid immunotherapy. Upon discussion with the clinician and review of the medical record, we learned that the patient was not treated with anti-amyloid immunotherapy. Given the findings of vasogenic edema, sulcal effusions, and innumerable microbleeds here, the most likely diagnosis is that of cerebral amyloid angiopathy related inflammation.

This patient on anti-amyloid immunotherapy underwent a post-dosing MRI where in the right frontal lobe we see on SWI, a new area of signal loss consistent with superficial siderosis. Since we only have one area of superficial siderosis, this would be a case of mild ARIA-H.

In the next case, the interesting part here is the history. The patient has history of uncontrolled hypertension and new onset of seizure. Although we see findings of cortico-subcortical signal change in the frontal lobe, in the parietal lobe, and temporal lobe that could look a lot like findings of ARIA-E in that setting, the diagnosis that we are leaning towards is that of posterior reversible encephalopathy syndrome.

This patient has history of dementia, however, the clinical presentation is that of a left-sided weakness for the past few days. On MRI, we see an area of cortico-subcortical signal abnormality on the right on the FLAIR image. On SWI, we just see some vague T2 hyperintensity, maybe a small amount of blood products. The key sequence here is going to be the effusion, the trace image, and the ADC, where we see an area of hyperintensity on the trace image with mixed signal intensity with some isointense and some hyperintense area on the ADC. On post-contrast imaging, we see gyriform enhancement. The clinical presentation together with the imaging findings, especially on the DWI are consistent with a subacute ischemic infarct.

**Dr. Cogswell:** Thank you for joining us on our session on ARIA Essentials in review of the imaging findings of ARIA, appropriate imaging protocols, the differential diagnosis for ARIA, and how to communicate findings of ARIA to referring providers.