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An Overview of ARIA: A Multidisciplinary Crash Course for Baseline Clinical Needs

Announcer:
Welcome to CME on ReachMD. This activity titled, An Overview of ARIA: A Multidisciplinary Crash Course for Baseline Clinical Needs, is jointly provided by Medical Education Resources and Efficient, LLC, and supported by an educational grant from Lilly. Before starting this activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Bateman:
Welcome to the ARIA Toolkit, an interdisciplinary curriculum. This program is designed to optimize team-based management of amyloid-related imaging abnormalities, or ARIA, and Alzheimer's disease. I'm Dr. Trey Bateman and it's a pleasure to guide you through this session.

The ARIA Toolkit is a multi-component curriculum designed to offer a comprehensive understanding of the complexities of ARIA. Throughout the curriculum we will engage in different interactive educational formats to equip you with the knowledge and skills needed to manage ARIA effectively. In today's session, our focus is on the latest advances in anti-amyloid antibodies and ARIA management, ensuring that you're prepared for real-world scenarios.

This curriculum is tailored to the diverse needs of healthcare professionals across specialties, including neurology, radiology, emergency medicine and primary care.

Our goal is to foster a collaborative, multidisciplinary approach, empowering each member of the care team to contribute effectively to the diagnosis, treatment, and management of ARIA.

Now, I'd like to introduce the expert faculty who will be leading our discussions and guiding us through the complexities of ARIA management. Once again, I'm Dr. Trey Bateman, Assistant Professor of Neurology, Psychiatry and Geriatrics at Wake Forest University School of Medicine. Joining me from neurology is Dr. Joy Snider, Professor at the Knight Alzheimer's Disease Research Center at the Washington University School of Medicine. Representing neuroradiology, we have Dr. Jerome Barakos, Director of Neuroimaging at Sutter Health in San Francisco. And bringing expertise for our colleagues in emergency medicine, Dr. Danya Khoujah from Advent Health in Tampa, Florida. And lastly, we have Dr. Charles Vega, Clinical Professor of Family Medicine and Associate Dean at the University of California, Irvine School of Medicine, representing primary care.

It's great to have you all here today.

Dr. Snider:
Thanks for doing this.

Dr. Barakos:
Yes, Jerry here, and a warm welcome to everybody with us here today, and it's a, really, an honor to be here with this distinguished panel of experts.

Dr. Khoujah:
Well, thank you so much for having me here. It's definitely going to be a great time discussing this and learning more from each other

and with each other, about ARIA.

Dr. Vega:
Hey everybody. Thanks very much for having me and thanks to our audience as well for joining us.

Dr. Bateman:
Right. Well, we'll jump in and get started.

Dr. Vega:
All right. Sounds great. So, these newer anti-amyloid, beta monoclonal antibodies. Very exciting. These are the first disease-modifying therapies that have been available for Alzheimer's disease, so we've been waiting for this kind of treatment for many years. Now, we have symptomatic therapies, as they're known, available: cholinesterase inhibitors and NMDA antagonist, memantine, but these are different. Their mechanism of action is that they can actually change the pathology of Alzheimer's disease. They are very effective, as we're about to see in a second, at removing amyloid beta from the brain, and they are also associated with cognitive benefits, which we're going to go into as well.

Now, there are some limitations, though. We want to make sure that we're identifying folks with cognitive impairment early because these multiple antibodies, while effective, are really best used and only indicated for folks with mild cognitive impairment and mild dementia. So, by the time you get more severe symptoms, unfortunately, the antibodies aren't likely to work anymore. There has to be confirmation that there is amyloid in the brain, so this means more PET scans. It might mean a lumbar puncture, so you need biomarkers to prove that there's amyloid-related disease before initiating these treatments and as I mentioned, early diagnosis is so critical even if you don't initiate monoclonal antibodies for Alzheimer's disease. One, just to give the option, but two, there's so much more we can do with folks when we diagnose them in earlier stages, and that's really on me in primary care to identify and then since that diagnosis.

So, the monoclonal antibodies are administered by intravenous infusion, but there are some cutaneous formulations in development, which would make the dosing a lot easier on patients, so that's very exciting.

And then, we're going to be talking about these amyloid-related imaging abnormalities, or ARIA. It's really the main, I think, side effect that we have to be concerned with across different specialties, and that's why there's such an esteemed group of folks from different backgrounds in terms of their medical specialty here today is because ARIA could actually touch all of us in terms of taking care of patients. And so, whereas there can be infusion reactions and perhaps some headaches, those are not as significant. And generally, these monoclonal antibodies are very well tolerated, but the ARIA is something we want to keep an eye out for.

Dr. Snider:
So, this is the data from the clinical trials on both the new antibodies that we have. They're called lecanemab, which was approved in 2023, and donanemab, which was approved in 2024. And as you can see from the two slide shown here, which are showing you the change in the amyloid PET. So, this is a PET scan that measures amyloid in the brain, and it gives you a number called the SUVRs, what they're using here, which shows you the overall amyloid in the brain. And what they're showing on the X-axis at the bottom is, over the time during this study, which was 79 weeks for lecanemab and 76 weeks for donanemab, what happened to the amyloid PET and the brains of people in the study? And for the people in the placebo group it didn't really change very much over the course of the study, and that's expected. When folks get to that stage of very mild impairment, MCI due to AD or very mild AD, the amyloid signal in the brain is pretty much maximal. It doesn't tend to go up during the course of the disease. And people on the medications, for both lecanemab and donanemab, there was a significant drop in the amyloid PET. What they're showing you is the change in the amyloid PET over the course of the study. And what's important to know is that at the end of both these studies, 70 to 80% of people that were on the medication basically had a negative amyloid PET. It looked like somebody without Alzheimer disease. So, these drugs were very effective at removing the amyloid from the brain.

This slide shows you how well these drugs worked clinically, and it's important to note that no one in these studies improved. Their memory and thinking did not get better. It did not reverse the changes of Alzheimer's disease. It did, however, slow the worsening that we see. And the scale used here is called the Clinical Dementia Rating Sum of Boxes, or CDR-SB. So, in both studies, they're showing this is going down. The actual absolute numbers going up, but they're showing you change. And what you can see is, as expected, folks in the placebo group declined. In the lecanemab study, the average decline was about 1.5, 1.6 sum of boxes, and in the donanemab study it was a little bit more. In both cases, however, the medication-treated folks declined less, and it's about 25 to 30% less, and this is basically about 0.5 sum of boxes. And so, one can think, well, is this clinically significant or not? What does this mean to patients?

And about a 0.5 sum of boxes, it occurs in about 6 different domains. But to give you an example, for example in the memory domain, this would mean that someone had slight memory loss. It was there, it was consistent, but it didn't really interfere with activities,

whereas someone at a higher level, a 0.5 higher level, would need reminding about appointments and would have more consistent memory loss. So, it's not a huge change, it's not a cure. It's not stopping progression, but it may be something that patients and families notice and something they would value.

Dr. Barakos:
Now, turning to the MR imaging, it turns out that treatment with these agents is very imaging-intensive. Now, on these timelines, we're seeing the T. These are times at which the patient is receiving therapy. You can see lecanemab is being administered as a dose infusion every 2-weeks, as opposed to the donanemab, which is once a month. So, those are the T's as we move across those timelines. What you'll see below that is the recommended times for what we call surveillance or monitoring MRIs. And you can see that the use of these agents is quite intensive. For example, with these agents in the first year or so, these patients will receive at least 5 monitoring MRIs. Now, the reason we use these MRIs is that the presence of one of the most significant complications, namely ARIA, tends to be clinically asymptomatic, so the majority of patients who develop this ARIA, which we'll talk about in greater detail, they're clinically asymptomatic, which means we need to use these surveillance MRIs to identify this finding to ascertain whether they should receive additional drug or whether there should be a suspension in terms of the drug administration, due to the presence of the ARIA.

Dr. Bateman:
So, the two drugs that we've talked about here, lecanemab and donanemab, the dosing is a little bit different between the two. Lecanemab is straightforward, it's 10 milligrams per kilogram and that's delivered every 2 weeks over approximately 1 hour. Donanemab, on the other hand, has an escalating dosing schedule, so it starts at 700 milligrams and it's given every month - every four weeks rather. That 700 is done for 3 weeks and then, the dose is increased to 1,400 milligrams and that's continued to be given every 4 weeks. It's a little bit shorter infusion time over about 30 minutes. And one of the notable differences between the two is that with donanemab, because of the way the trial was conducted, there was a unique protocol that allowed for potentially, discontinuing the therapy if a repeat amyloid PET scan showed that there had been a significant reduction in amyloid plaques, down to the point where folks would be considered negative on their amyloid scan.

Dr. Vega:
So, the good news is that Medicare is covering these monoclonal antibody agents. Clinicians who are prescribing the agents, and administering them, need to be part of a registry. I think it's actually very beneficial to have a registry to get more data on safety and efficacy over time, as well as just ways we could support one another with some of these complicated issues like ARIA.

And in addition, remember, this is going to require extra imaging. So, we are requiring biomarkers such as a PET scan for patients, so CMS has expanded their coverage for PET scanning and you really do need a baseline MRI of the brain and follow up MRIs of the brain. So, patients who can't undergo an MRI for a number of reasons – I have some of my my patients who still have loose metal in their bodies and just aren't going to qualify for an MRI. That would be a difficult task for patients and maybe a nonstarter for them. But their payment structures are in place, so we could support our patients to get monoclonal antibodies.

Dr. Barakos:
Now, turning to the topic of ARIA. As you've probably heard, ARIA is an acronym that stands for amyloid-related imaging abnormalities, and it really is that. This is a process in which, on MRI, we can see changes in the brain that's related to the mobilization of the amyloid by these agents. Now we divide ARIA into two types.

E, standing for an effusion, or an exudate, and H, which is a hemosiderin or a heme-type change. So, in other words, when there is mobilization of amyloid, there's kind of a transient reduction in the structural integrity of the vasculature that can allow some fluid to actually leak out from these vessels, and when it leaks out into the brain parenchyma, that can present as vasogenic edema. Whereas if it leaks out into the left meninges of the brain, that can present as a sulcal effusion.

So, that's where we get the E, is a fluid is leaking out of the vasculature.

When blood product actually leaks out, it typically will present in the parenchyma as micro hemorrhages. The are punctate foci of blood degradation product measuring 2 or 3mm in diameter. Or, if this leak takes place in the left meningeal structures of the brain, that'll present a superficial siderosis. So, we have the two types, the ARIA-E referring to the fluid aspects of this leakage, or the ARIA-H referring to hemosiderin product that's either in the brain or on the surface of the brain.

Dr. Khoujah:
So, the question is, how prevalent are these ARIA? In the lecanemab trial, 13% of the patients who are getting the drug had ARIA-E versus 2% of those getting the placebo. In the donanemab study, it was 24% versus 2%. Seventeen percent of those who got lecanemab got ARIA-H, versus 9% of those who got the placebo. As for the donanemab study, it was 31% versus 13%. And I know these numbers look like they're kind of big, but those are all of the ARIA when we're talking about symptomatic, asymptomatic, just the

stuff that's showing up on MRI, and so on.

The stuff that really matters to us in clinical practice is more the symptomatic ones. So, what do these look like? For lecanemab, there were 3% of the patients who got the drug. As for donanemab, it was 6%. Less than 1% of those without lecanemab had serious ARIA, and as for donanemab, it was less than 2%,

So, looking at all these numbers, most ARIA is one; asymptomatic, and two; even if it was symptomatic, it's usually non-severe.

Dr. Bateman:
So, let's talk about some of this now. How does – I'd be interested in everybody's thoughts - How does the available clinical trial data for lecanemab and donanemab risk of symptomatic ARIA compare? Right? So, we saw that there were a little bit of differences in the numbers. What do folks make of that?

Dr. Snider:
I'll start off. I think we'll talk in a few minutes about APO-E and how that impacts risk of ARIA. So, I think for decision-making, it always comes down to a discussion with a patient and their family about what the benefit means to them and what risk they're willing to accept. And I think we do that, really, based on APO-E and it becomes a shared decision between the physician and the patient. And where we run into some disagreements among physicians is which patients we should even offer these treatments to, and I think we may get into that in a little while. But I think you do have to look at them. Maybe in the longer term we'll find out they're not that different. You did notice there was a little difference in the baseline ARIA-H rate in two groups. There was a slightly different selection in the trial, so maybe there was something different about the patients. But right now, the data we have suggests that donanemab has a somewhat higher rate of ARIA. It does have a lower rate of infusion reactions, which again, are usually not severe, but for some patients are really bothersome, so that might weigh into some people's decision as well.

Dr. Vega:
I'll just contribute that I think when we think about these anti-amyloid antibodies, we have a big upfront task in counselling patients and overcoming the discussion of ARIA because frankly, in primary care when patients here, wait, brain hemorrhage or swelling? That's a big barrier right there. And so, I think it's important to contextualize it that most of these cases are not symptomatic, you won't feel any different. It might relate, or might result, rather, in a stoppage of the drug for some time and then re-observation with MRI, but most patients can continue forward, and serious side effects are quite rare. And then, bring in the benefits of these agents in terms of cognitive improvement, as you discussed, Joy. And so, but I will say, compared with other things we may discuss in primary care when we're talking before the patient gets to the neurologist, or maybe they saw a neurologist and they called me back and said, hey, they're talking about this new injectable therapy. I'm not sure, what do you think about it? I think it is a bit of a challenge with some of the numbers and particularly, the subject material, and my job is to put it in a realistic context and discuss benefits versus risks just like any other intervention we do.

Dr. Snider:
So, who is at higher risk for ARIA? We touched on this a little bit a minute ago. But the big risk factors fall into a couple of categories. Number one is APOE4. So, apolipoprotein-E, as most of you probably know, is a risk factor for Alzheimer's disease and many cardiovascular disease, head injury, and it plays a big role in ARIA risk. People with one or more APOE4 alleles are at higher risk than folks without, and those with two APOE4 alleles are at higher risk than those with one. And those numbers vary with the two different medications, but it's important to counsel your patients based on their specific risk. So, for that reason, we do recommend very strongly that everyone have APOE testing, and then we can counsel them on their specific risk with these agents.

Another big predictor is baseline MRI findings. So, the clinical trials were done with some very specific parameters where people with more than 4 microhemorrhages, or more than two areas of superficial siderosis were excluded from the trial, as were people who had large strokes or who had had a macro hemorrhage in the past. So, it's very important to get a good baseline MRI. And some MRIs are not – not all MRIs are equal. I'll put it that way. So, it's very important to make sure your MRI includes hem-sensitive sequences. These can be either GRE or SWI, but you really need a collaboration with a really good neuroradiologist and someone who's comfortable reading these scans.

The microhemorrhages are in fact micro, so they're really tiny. And sometimes, you might not see them clearly on the baseline MRI. You might see them on the follow-up MRIs better, so we do allow more than 4 microhemorrhages going forward in this study, but you really want to make sure you don't have more than that at baseline.

And then, the other types of things are time. So, for both these medications, it varies a little between the two of them, but the microhemorrhages, the hemorrhages and the edema tend to occur early on, so that's why the MRIs are stacked up early on in the treatment process. So, that's why we follow the very specific schedule as recommended for the MRIs.

The more controversial aspect is antithrombotic medication. So, in both these clinical trials, folks were allowed to be on antiplatelet agents, aspirin, and even anticoagulants. And in both in the lecanemab study, there were some people who were on anticoagulants, mostly Coumadin. Two people in the treatment arm did develop macro hemorrhages. This was higher than expected for people on those anticoagulation medications, so some people believe we should exclude people on anticoagulants from taking these medications. That is written in the appropriate use criteria that were drafted by a group of Alzheimer experts but is not universally agreed on. And we can talk more about this later, but I do have patients both in the clinical trials and in practice who are on anticoagulants and have elected to take these medications. But again, it requires a very frank discussion of risk versus benefit and a discussion of what we don't know about the risk.

We know it's higher, but so few people were treated with these in the studies, we don't really know how much higher. So, it's important to discuss what we know and what we don't know and it's important to collect data, so that's why these registries are important.

Dr. Khoujah:
So, what does ARIA look like clinically? As we talked about before, a lot of it is asymptomatic. And the symptoms can be mild or severe. They can be things like headache, confusion, dizziness, vision changes, nausea, aphasia, weakness or seizures. So, depending on how severe these symptoms are, we might think that some of the differentials are some of the scarier things, and that's what we think about in the emergency department. When you see patients who are coming in with severe neurological symptoms, we think maybe they're having an acute ischemic stroke. Maybe they're having an intracranial infection, a subarachnoid hemorrhage, posterior reversible encephalopathy syndrome, or PRES. And that is why ARIA is very important for everybody to understand, especially in the emergency department where they're presenting with severe symptoms because they can mimic several other neurological disease processes. Things that are very time sensitive and they're very critical. Again, that is not common. The likelihood that the patient's going to have a severe ARIA is much lower than any ARIA or asymptomatic ARIA, but it is there.

Dr. Bateman:
To talk about this a bit more, many of the symptoms of ARIA are mild, and like you pointed out, they mimic other conditions, and so the differential is broad. It can be confused with other conditions. In practice, how is this going to complicate the recognition of ARIA and how is it going to complicate how this is getting managed in the real-world?

Dr. Snider:
Trey, you're exactly right. As I was telling you, these symptoms can mimic other things and they can also – One of the main symptoms that we see in the trial and also in practice, is confusion, and patients with mild Alzheimer's disease are not typically extremely confused, but there can be a little of that, and sometimes it's hard to dissect whether they're more confused in a significant way or not. So, the main response when you're concerned about ARIA – I mean, if it's severe, we certainly send patients to the emergency room. But the key thing is we get an MRI scan. So, they're scheduled MRI scans during the use of these medications, and then if you have a suspicion of ARIA, you can get an unscheduled MRI scan and just make sure if there is ARIA or not. So, it helps to have a very low threshold to do an MRI scan. I think we'll learn more as we go on, and maybe be able to fine tune that a little bit. But if you're suspicious, it's important to get an MRI scan and look for that. And important to educate patients to let you know when these things happen. So, it does complicate recognition and management. It does mean you need to have someone available for the patients to call and find out if this is ARIA or not, so that's been an exciting change in our practice being on-call.

But it is just important to be sensitive to it. And hopefully as time goes on, we'll become better at figuring out when it's symptomatic ARIA versus not.

Dr. Khoujah:
As you said, Joy, I think communication is going to be really essential moving forward be to help us improve our recognition and management of ARIA. I think the first thing that we got to do is first of all, understand and know that these patients are on these medications for us to recognize that ARIA is even a possibility. So, when there's that great communication cycle between the patient and their neurologist who's prescribing these medications, the neurologist may call ahead to the emergency department to ensure that communication happens. Now, with the advent of electronic communication, that can also happen between the patient and their neurologist, the neurologist and the emergency department, and that would ensure that we think of it. Just like they say, the eye will not see what the mind does not know. If we don't even recognize that the patient is on this medication, then we're not going to recognize that ARIA is even a possibility, and that's why it would not pop up on our differential, we would not think about it. We would think, oh, they're confused because of delirium, they're confused because of progression of disease, or something else. Or if they were to present in something that's a little more time sensitive, we would be so caught up in that thing, whether we're thinking it's PRES or a stroke or a bleed, that thinking of ARIA is not going to come to the forefront of our mind. So, I think the first thing is, as you said, communication.

Dr. Vega:

Yeah, absolutely. That is so important. And I think that one way we can contribute in primary care is, we've often known the patient for years and we know their premorbid functioning, so when we think about their level of cognitive impairment, we also know other chronic conditions they may have. Maybe they have chronic tension headaches or migraine, Maybe they have a neuropathy with numbness and tingling. And Danya, I'll say that you can call us anytime in primary care. I'll always take a call from the emergency department because we can really clear this stuff up. Yes, you're on a monoclonal antibody. Yes, they've had that bilateral foot numbness for at least 18 years now, and that's why they're on two drugs for it. And that can be very helpful in shared decision-making. I absolutely think we have to be sensitive to the possibility of ARIA, and those really important symptoms will make some important findings, getting neuroimaging on those patients. But there's also a lot of patients where I think we could find out, like lo and behold, this is actually the same as they were yesterday and two years ago and probably lowers our risk of over-imaging individuals.

Dr. Bateman:
We've had a lot of discussions in our practice with folks that have, as you said, tension headaches. They've had headaches for years, they have a headache every week or two.

And I think what Joy pointed out is, that low index of suspicion. The chances are, some of those patients are going to get normal MRIs when we're concerned that those headaches doesn't represent ARIA this time. And I think it's a little bit of a dynamic target for folks as we get more comfortable and better understand when our index of suspicion should be even higher. It seems to be a complication that we're all having to learn to navigate in real clinical practice.

Dr. Barakos:
Well, let's take a look at some examples of ARIA. Now, on the lefthand side of the screen we have two examples of the ARIA-E. In the upper lefthand corner, we can see a large area of edema. Now, one point that was brought up, which is very important, that this ARIA-E is reversible. This is a transient edematous process that resolves without residua. So, it's a transient phase during the early phases, typically, of drug administration when we have this transient loss of structural integrity of the vasculature. So, this is a transient process and it resolves. And the vast majority of the time, it's asymptomatic. And that is why imaging is so critical. For example, the patient on the upper lefthand, we see a large area of edema, vasogenic edema, basically. If this patient was in our routine clinical practice unrelated to nonamyloid administration, what would bring them to clinical attention would be clinical symptomatology. This patient will come in because they were having seizures or neurocognitive issues. But with the anti-amyloid therapy, they tend to have no symptoms and this is why imaging is critical.

Now, this patient has an extensive amount of vasogenic edema, and the last thing they need is more of this drug. But you wouldn't know that clinically because the patient's doing well from a clinical perspective. And again, highlighting the essential role of the routine surveillance imaging that takes place because this patient does not need more medication. And that's the role of these surveillance or monitoring MRIs.

Now, in terms of examples, in the upper lefthand corner we have the ARIA-E, which is the edema within the brain parenchyma itself. Below that, we have an example of a sulcal effusion where the fluid is actually leaking into the left meningeal spaces around the brain. And you can see that that pattern there, these images on the left, are the T2 flare sequences. These are the essential sequences that will optimize constituency of these edematous changes. So, it's a T2 flare sequence where suppressing normal water signal.

You can see that the picture on the lower left, to a neural imager or a routine radiologist, that would look like a subarachnoid hemorrhage, for example. So, that's why, as everyone has been outlining, clinical history is imperative. Because if someone saw that and didn't know the clinical history, that's a subarachnoid hemorrhage until proven otherwise, and is actionable. This patient may undergo a lumbar puncture.

However, if there's food communication between the caretakers, you would understand that A; maybe the patient doesn't even have headaches, has no nuchal rigidity, no symptomatology to suggest a subarachnoid hemorrhage. And guess what? They happen to be on an agent that just happens to result in a process called ARIA that can look just like this. So, as in all aspects of medicine, clinical history is imperative and more so for the radiologist in cases like this, because remember, at the end of the day, when not treating the films, we're treating the patient. So, understanding what the clinical scenario is, is paramount.

Now, on the right part of the screen we have the ARIA-H examples. Now, remember, as outlined, these are blood degradation products, and you're not going to see these if you're not using a blood sensitive sequence. So, you need a GRE T2 star or susceptibility weighted sequence. These areas of signal abnormality will not be seen on routine T1, T2, or T2 flare. Now, the microhemorrhages, we've kind of been using the terms microhemorrhages and hemorrhages a little bit interchangeably. Associated with these anti-amyloid agents, if we have ARIA-H, we expect microhemorrhages, not macro hemorrhages. Macro hemorrhages are typically related to other pathologic conditions which may be comorbidities like underlying CAA or other conditions.

So, when we talk about micro hemorrhages in this context, we're talking about lobar microhemorrhages. And as you can see in the top example here, we see a few small dark foci and this represents were some red blood cells have leaked out into the parenchyma and we can see it presenting as these microhemorrhages.

Now, in the image below, we can see a little area circled which demonstrates some superficial siderosis. These areas of blood product were not noted on the baseline scan, but only on the follow-up scan, so they were incident developed areas of siderosis. So, there we have it. We have four different examples with ARIA-E, either have fluid leaking out, and if it's in the parenchyma, we call it ARIA-E edema. If it's in the left meninges, it's a sulcal effusion. Whereas the blood product, if it leaks out into the parenchyma, we have a microhemorrhage, lobar microhemorrhage, or if it leaks out into the left meningeal areas, it'll present as an area of superficial siderosis.

Dr. Bateman:
So, as we've been saying, the care roles in ARIA span multiple different specialties; primary care, the Alzheimer's disease specialist, emergency medicine specialists and our radiology colleagues. And so, let's hear a bit from each role here, and how their care-role is seen within taking care of ARIA.

Dr. Vega:
Well, so there's some overlap, as you saw there in that graph. It is a puzzle. But yeah, I believe that patient education support. This is a specialized treatment and it's really going to be given for – currently, it's mostly limited to specialty centers.

But patients are going to come to you and ask about it, and so therefore, hopefully, this program gives you the knowledge so that you understand what the benefits of monoclonal antibody treatments are for folks with Alzheimer's disease and mild cognitive impairment are, and then what are some of the risks. Particularly with ARIA. I think it's great we could go over the schedule of how we monitor for ARIA. We can support patients in getting their MRIs on time. Patients, as I mentioned, who call in and they have symptoms, we might be the first call. They might be going to the emergency department, they might be going to a neurologist, and it is really important to communicate that and get the appropriate response going if it's additional imaging. Maybe it's they need to come in for a clinical exam. But we really want to let the entire care team know and then, follow them up over time to make sure that those – Say, they developed ARIA, they go off schedule, perhaps they get a pause in their treatments with monoclonal antibody. Many times when we're talking about folks with cognitive impairment, this could be a daunting schedule. They may not remember, oh, I've got to go back for this other appointment for another MRI or another visit to the neurologist. And so, we want to keep them on track there as best we can, as well.

Dr. Khoujah:
As for emergency medicine, it's important for us to one; recognize that the patient is on anti-amyloid monoclonal antibody through accurate medication reconciliation, which to be honest, can be a beast, especially when patients are on multiple medications and, as Chuck noted, they have an element of cognitive impairment. Sometimes asking a really simple question of, do you have to go somewhere to get injections for any of your medical problems can help. Or does somebody have to help you with some of your medications? And then, we need to identify the signs and symptoms of ARIA and develop a comprehensive differential diagnosis. And as we've been talking about before is, interdisciplinary communication is essential for this to be recognized and managed. One; we need to communicate pretty clearly with radiology that the patient is on a monoclonal antibody and that we are concerned for ARIA. Because like we talked about before, run-of-the-mill MRI is not going to pick up what we need. It needs to be the correct type of MRI with the correct sequences.

I'm an emergency physician. I know to order an MRI, and I need help from my neurologists, my radiologists, to help me figure out what exactly I need to order. I need to communicate that so we can pick up these conditions. And what's important is also, if we have any baseline MRI results, to share that with our radiologists. Sometimes they may not have access to all of this information and communicating that is going to be essential.

Communicating with the patient's neurologist is also pretty important, if we have access to them. We need to also ask our neurology colleagues what type of medications the patients are on exactly. What's their treatment timeline?

And try to figure out and communicate with them after the end of this assessment whether we did find ARIA or not to allow them to figure out whether they can continue this treatment outside of this emergency department visit.

After communicating with our colleagues, at that point we're going to be able to order the appropriate imaging and diagnostic tests. And finally, we need to consult with our colleagues for inpatient admission or for discharge. If we do end up admitting the patient for their complaints, we need to consult with our neurologist that's in-house to determine the necessity of that inpatient admission based on the ARIA severity. And if that's different from their neurologist, they probably need to communicate together and figure out what are the next steps. If we are discharging the patient, then we definitely need to make sure that they have appropriate follow up with their neurologist, and perhaps their primary care doctor as well.

Dr. Barakos:
Now, the radiologist also has a very important role at many different stages in the treatment of these patients. First off, we have the role of the baseline MRI. It turns out that patients must meet certain imaging criteria before they can be considered candidates for these agents. In brief, what we're trying to do as radiologists is exclude patients who have a potential condition of cerebral amyloid angiopathy from being treated with these agents, because if you have CAA – which can also be reflected by having being a homozygous APOE, you have higher risk. Those are the patients who tend to have the highest risk of complications.

So, what are we doing as imagers? Well, as you'll see on the package inserts, and for most of these trials, we exclude all patients who have more than 4 lobar microhemorrhages. Now, note, when we're talking about microhemorrhages, we're specifically addressing lobar microhemorrhages. These are the microhemorrhages out in the, pretty much, the substance of the cerebral hemisphere, not the deep gray matter structures. Those microhemorrhages, or hemosiderin deposition, or mineralization of the deep gray matter, that tends not to be associated with what we're talking about here. That tends to be more microangiopathic related to vascular risk factors, which is not a risk factor for having a complication. So, in brief, in the baseline MRI, the radiologist is looking to exclude patients who have more than 4 lobar microhemorrhages or areas of siderosis, leptomeningeal siderosis, because those are the hallmarks of patients who most likely have cerebral amyloid angiopathy. So, basically, we're using the Boston criteria. If someone were to have lobar hemorrhage or history of large hemorrhage or large stroke, again, those patients would typically be excluded.

So, that's the role in terms of the baseline MRI. Then, we have the routine monitoring MRIs we've talked about, where the patient comes in at specified protocol time intervals that differ between the agents, and our role as radiologist is to be looking for ARIA. And ARIA can be quite subtle.

The important point here is, when the radiologist is looking at one of these surveillance MRIs, we're in a position to give a go/no go for the next infusion. And literally, most of the time there's a patient and a physician waiting for that result to determine whether that patient will receive the infusion. Because if the patient does have ARIA of a certain extent, that would suggest that this patient should not be dosed. Now, in certain cases if it's mild, you may dose through the patient. But the point is, the radiologist needs to identify if there's ARIA and accurately communicate that information in a timely fashion to the physician caring for the patient.

Now, this brings up an important point. Since ARIA can be very subtle, either the ARIA-E or the ARIA-H, you have to make a close comparison to the baseline scan because sometimes you wouldn't appreciate the abnormality if you just looked at it one time-point. Now, on the lower lefthand side here, we have something called out-of-sequence MRIs, and this brings up an imperative point. We do have the routine scheduled MRIs. However, if at any point in time the clinician feels that there's some change in the patients clinical status, that could represent ARIA or some other pathologic process. And that brings up an important point, is when these patients are on these agents, it doesn't mean the only pathology they'll ever get is ARIA. They can succumb to the same issues any patient can, whether it's a subarachnoid hemorrhage, a stroke, other parenchymal abnormalities. So, it's imperative to keep your differential open, but at any point in time, if there is concern for a change in the clinical status, you can order an MRI and then of course, the radiologist is again looking to determine might this be ARIA or might this be another pathologic process.

And finally, we have long term follow-up. As has been described, the majority of ARIA will take place in the first 6 or 8 months or so of treatment. However, we've seen ARIA develop actually, 2 or 3 years out. It's quite infrequent, but it always remains a risk.

Dr. Snider:
The role of the neurologist, or Alzheimer disease specialist, in all this is to, in general, do the initial assessment, evaluate the baseline findings, discuss with the patient the risk and benefits of the therapy, and decide if the patient's a good candidate or not, and along with them, to initiate the treatment. So, this involves initial assessment of that baseline MRI, working with the radiologist and understanding what the patient's risk and benefits are.

After that, the specialist does assess those acute symptoms as they come up and gets calls from the patients and families if there are concerns, and decides in consultation, either with the primary care docs, as we've heard from Chuck, if we need to do something more. And that can range from getting an initial MRI to see if there is ARIA to sending a patient to the emergency. So, it's very important for the specialist to be available, to be communicating with the patient, and to be able to refer them as appropriate for those management findings.

We continue to review the MRIs, and as Jerry pointed out, it's really important to get timely reads on these MRIs, as well as to get the appropriate things noted on the report. So, we want to know if there is ARIA, and we also want to know if there's not ARIA. So, our radiologists have been very good about templating their reports to now include that, so we know if it's there and we know if it's not there.

We sometimes do suspend dosing and there are guidelines for this in the package insert. But as Jerry mentioned, if it's mild ARIA that's asymptomatic if it's just one or two microhemorrhages or a tiny area of edema, we can dose through that and the patients do very well.

But if it's more severe, we hold dosing and we can either suspend dosing temporarily or suspend it permanently. Generally, we will repeat the MRI in about 4 weeks, which might be too soon, but that's the current guidelines. Generally, ARIA resolves. Again, as Jerry pointed out, within at least 2 months. Sometimes it takes 3 months, but generally it resolves, so we continue with the ongoing management.

And then, we monitor the patients long-term. We really want to know in the real-world how these patients do, so we want to continue to assess their cognition, see how rapidly they progress. The key role, and I think we've all emphasized this, is communication, and it's important to communicate between providers. Sometimes the electronic medical record can help with this. Our EMR has been set up to flag patients who are on these treatments, but if your patients go to a different healthcare system they may not get those flags, so again, key communication is important. Making the patients and their caregivers aware that they're on these drugs. Giving them a laminated card, or some people use a wristband, whatever you want to use, so they have something that states clearly that they're on these medications.

Dr. Bateman:
So, that concludes today's session. I'd like to extend a thank you to our expert faculty for sharing their insights and guiding us through the intricacies of ARIA management.

Dr. Snider:
Thank you, Trey. It was a great pleasure and I learned a lot from everybody. I hope our listeners did as well.

Dr. Barakos:
Yes, thank you everyone. A pleasure.

Dr. Khoujah:
Thank you. It's been an absolute pleasure.

Dr. Vega:
Great session. Thanks very much. And thanks to our audience as well.

Dr. Bateman:
I want to remind everyone that today's session is just one component of the ARIA Toolkit curriculum. We encourage you to keep an eye out for these sessions as they will offer further opportunities to enhance your expertise in managing ARIA across different clinical settings. Thank you for participating in this collaborative effort to advance the care of patients with Alzheimer's disease.

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