Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/early-alzheimers-disease-treatment-assessing-patients-and-coordinating-care/26537/

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Early Alzheimer's Disease Treatment: Assessing Patients and Coordinating Care

Narrator:
Welcome to ReachMD. This medical industry feature titled "Early Alzheimer's Disease Treatment: Assessing Patients and Coordinating Care" focuses on treatment with LEQEMBI® (lecanemab-irmb). This program is sponsored by Eisai Inc., and Biogen, and is intended for healthcare professionals. Now here are your hosts, Dr Justin Moon and Dr John Bertelson.

Dr Moon:
I'm Dr Justin Moon. I'm a neurologist and the director of the Denver Neurological Clinic.

Dr Bertelson:
I'm Dr John Bertelson, a behavioral neurologist. I see patients at the University of Texas in Austin, a clinic at Texas Tech, and I have a private practice also here in Austin.

Dr Moon:
We're going to share with each other, and our audience, how we walk through patients and their loved ones through the journey with LEQEMBI.

Narrator:
Summary of Important Safety Information

INDICATION
LEQEMBI® [(lecanemab-irmb) 100 mg/mL injection for intravenous use] is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.

BOXED WARNING: AMYLOID-RELATED IMAGING ABNORMALITIES (ARIA)

SUMMARY OF MOST SERIOUS AND MOST COMMON RISKS ASSOCIATED WITH LEQEMBI
CONTRAINDICATION: LEQEMBI is contraindicated in patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS: ARIA; HYPERSENSITIVITY REACTIONS; INFUSION-RELATED REACTIONS

MOST COMMON ADVERSE REACTIONS: infusion-related reactions, ARIA-H, ARIA-E, headache, superficial siderosis of central nervous system, rash, and nausea/vomiting

Please stay tuned for additional Select Safety Information at the end of this podcast, and accompanying full US Prescribing Information including **Boxed WARNING**.

Dr Moon:

When considering appropriate patients for the treatment with LEQEMBI, the first questions we ask are: Would the patient be interested in such a therapy? Are they at earliest stages of disease? Are there any significant factors that might exclude them?

Dr Bertelson:
In each of my clinics, we get a history from the patient and a member of their family, if available. So you do your examination, which not only is checking balance, strength, reflexes, but also includes some sort of cognitive battery. There are several well-known tools to choose from, but they should be adequately sensitive to MCI. If one hasn't been done already, I suspect most neurologists would order an MRI.

Dr Moon:
In our clinic, we do an initial MRI and basic labs, as well as an EEG and bedside memory evaluation. Upon their return visit, they would have the memory test first thing in the morning to get an accurate memory evaluation. Then, we would assess the patient and try to determine whether this pattern seems consistent with a progressive neurodegenerative process.

Dr Bertelson:
I also think the appropriate candidates for LEQEMBI have a reliable caregiver or someone in their life who can speak up if the patient has a complication and if they're unable or unwilling to report it. We also have to consider other things, such as concomitant medications. We are particularly cautious when patients are on certain blood-thinning agents. They should have ApoE genetic testing, so that we can better understand their individualized ARIA risk.

Dr Moon:
When we look at patients, particularly from a vascular standpoint, we also look for those who have less disease. We feel more comfortable treating those patients. An optimal patient, to me, is someone who comes in and identifies their problem at an early stage. They have mild deficits on memory testing, very mild atrophy on MRI, but they have confirmatory tests that suggest AD pathology.

Confirming amyloid pathology is the next step for making the diagnosis of Alzheimer's disease. We say, "These are the next tests to see if we have the pathology that the newer therapies target." And then we talk a little bit more about the medication. When we get to the confirmatory test for amyloid beta, then we really talk heavily about therapy and potential treatment options available.

Dr Bertelson:
Generally, in the second visit I can say, "Okay, I suspect this might be Alzheimer's disease. There are treatments that have been available for 20 years that we should consider, but there's also an agent that I'm particularly excited about." Depending on their response, we might then proceed with a spinal tap or amyloid PET to look for amyloid pathology. I will also order ApoE testing if this hasn't been already done.

Dr Moon:
After we have completed the workup, we want to start thinking about treatment. I start off by saying, "As this disease progresses, we may encounter more problems with memory and day-to-day function." Then I start talking about what we can do.

We talk about how it's an infusion therapy that they would be given every 2 weeks and that the purpose of the medication is to remove toxic soluble amyloid aggregates and plaques that are believed to cause the disease. I do caution them that LEQEMBI is not a cure, and it will not bring back their memory, but I tell them, "This may allow you or your loved ones to take steps to slow down how fast the disease is progressing."

They may ask, "Is this forever?" I tell them, "This is a continuous disease process that may require continued treatment, and that we can use our clinical judgement and make a decision together about when it's time to stop." We, as clinicians, know that even after amyloid plaque is removed, the disease doesn't stop—neurotoxic soluble amyloid aggregates, like protofibrils, continue to form.

Dr Bertelson:
I've got a dry erase board, and I sometimes use that to replicate the graph from the Phase 3 study where you see the split in disease progression as time goes on between the treated and untreated people. And again, I say, "It doesn't make you better, but it slowed the decline compared to people who were otherwise untreated."

I have a nurse practitioner and a physician's assistant who coordinate the nuts and bolts of the infusion process.

Dr Moon:
In working with outside infusion centers, it's key that you bring them into the conversation early. You have to sit down and talk to their

leadership saying, “This is what we're trying to do, this is what we need from you, and this is the expectation of our protocols.”

We have a wonderful team who understands this process. This involves nurse practitioners, who along the way help manage these patients; our medical assistants, who are aware where to send these patients for testing and to follow them up; our radiologists, who have been trained to look for ARIA; and our infusion colleagues, who understand that they are a checkpoint if that patient needs to stop, pause, and get that MRI before we continue infusions.

As LEQEMBI becomes more broadly used, and as radiologists in different sites and infusion centers at different places get more familiar with this, this will become more standardized in the community.

Dr Moon:
LEQEMBI can cause ARIA-E and ARIA-H. ARIA-E can be observed on MRI as brain edema or sulcal effusions, and ARIA-H as microhemorrhage and superficial siderosis. I don’t think that all neurologists know that ARIA can occur spontaneously in patients with Alzheimer’s disease. We do see microhemorrhages and edema in untreated individuals. Even the placebo patients may have this.

Dr Bertelson:
I’d like general neurologists to better understand the concepts of ARIA-E and ARIA-H. Also, when you can, send patients to the same MRI time after time because there are often technical differences between MRI machines, especially when they are with different organizations. Make sure you’re communicating to the reading neuroradiologist that you’re looking for ARIA.

Dr Moon:
We had identified our radiologists early on, and we had them take a little bit of a deep dive in ARIA. This is something that we probably have to do on a regular basis to get new clinicians on board. Then, we talk to their leadership about what we're looking for and what we need from them in terms of how they communicate with us.

Dr Bertelson:
I would also encourage neurologists to communicate with the radiologist; they can’t just say that there are “some microhemorrhages”, or “a few”, or whatever. They need to actually quantify them.

Dr Moon:
In clinical settings, we are gaining confidence as we encounter an abnormality on the MRI. We are all learning this process as we’re doing it. A very important message to relay to the general neurologist is that most of the time patients don't even know it's happening to them because they’re asymptomatic, and that we're catching this on MRI.

Then our patients have a follow-up scheduled, so that we can have a conversation in person. We show them the abnormality. We say that this can be seen in normal healthy individuals, but because they are on medication, there are considerations. Then, we decide together on whether we're going to continue. We show them the general recommendations from the LEQEMBI® Prescribing Information. If they are safe to continue from those general recommendations, we say we think we can continue and we will monitor you closely and reassess in another month.

Dr Moon:
I hope you feel more confident that you can take these steps to identify, treat, support, and counsel appropriate patients and their families.

Dr Bertelson:
It’s our responsibility to guide them through the journey with LEQEMBI.

For more information about LEQEMBI, visit www.LEQEMBIHCP.com.

Narrator:

IMPORTANT SAFETY INFORMATION

WARNING: AMYLOID-RELATED IMAGING ABNORMALITIES (ARIA)

- **Monoclonal antibodies directed against aggregated forms of amyloid beta, including LEQEMBI, can cause ARIA, characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). Incidence and timing of ARIA vary among treatments. ARIA usually occurs early in treatment and is asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. Serious intracerebral hemorrhages >1 cm, some fatal, have been observed with this class of medications.**
  - **Apolipoprotein E ε4 (ApoE ε4) Homozygotes: Patients who are ApoE ε4 homozygotes (~15% of patients with AD) treated with this class of medications have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed, they can still be treated with LEQEMBI; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.**
- **Consider the benefit of LEQEMBI for the treatment of AD and the potential risk of serious ARIA events when deciding to initiate treatment with LEQEMBI.**

CONTRAINDICATION

LEQEMBI is contraindicated in patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

AMYLOID-RELATED IMAGING ABNORMALITIES

Medications in this class, including LEQEMBI, can cause ARIA-E, which can be observed on MRI as brain edema or sulcal effusions, and ARIA-H, which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with AD, particularly in patients with MRI findings suggestive of cerebral amyloid angiopathy (CAA), such as pretreatment microhemorrhage or superficial siderosis. ARIA-H generally occurs with ARIA-E. Reported ARIA symptoms may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms usually resolve over time.

Incidence of ARIA

Symptomatic ARIA occurred in 3% and serious ARIA symptoms in 0.7% with LEQEMBI. Clinical ARIA symptoms resolved in 79% of patients during the period of observation. ARIA, including asymptomatic radiographic events, was observed: LEQEMBI, 21%; placebo, 9%. ARIA-E was observed: LEQEMBI, 13%; placebo, 2%. ARIA-H was observed: LEQEMBI, 17%; placebo, 9%. No increase in isolated ARIA-H was observed for LEQEMBI vs placebo.

Incidence of ICH

ICH >1 cm in diameter was reported in 0.7% with LEQEMBI vs 0.1% with placebo. Fatal events of ICH in patients taking LEQEMBI have been observed.

Risk Factors of ARIA and ICH

ApoE ε4 Carrier Status

Of the patients taking LEQEMBI, 16% were ApoE ε4 homozygotes, 53% were heterozygotes, and 31% were noncarriers. With LEQEMBI, ARIA was higher in ApoE ε4 homozygotes (LEQEMBI: 45%; placebo: 22%) than in heterozygotes (LEQEMBI: 19%; placebo: 9%) and noncarriers (LEQEMBI: 13%; placebo: 4%). Symptomatic ARIA-E occurred in 9% of ApoE ε4 homozygotes vs 2% of heterozygotes and 1% of noncarriers. Serious ARIA events occurred in 3% of ApoE ε4 homozygotes and in ~1% of heterozygotes and noncarriers. The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers.

Radiographic Findings of CAA

Neuroimaging findings that may indicate CAA include evidence of prior ICH, cerebral microhemorrhage, and cortical superficial siderosis. CAA has an increased risk for ICH. The presence of an ApoE ε4 allele is also associated with CAA.

The baseline presence of at least 2 microhemorrhages or the presence of at least 1 area of superficial siderosis on MRI, which may be suggestive of CAA, have been identified as risk factors for ARIA. Patients were excluded from Clarity AD for the presence of >4 microhemorrhages and additional findings suggestive of CAA (prior cerebral hemorrhage >1 cm in greatest diameter, superficial siderosis, vasogenic edema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of ICH.

Concomitant Antithrombotic or Thrombolytic Medication

In Clarity AD, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed if the patient was on

a stable dose. Most exposures were to aspirin. Antithrombotic medications did not increase the risk of ARIA with LEQEMBI. The incidence of ICH: 0.9% in patients taking LEQEMBI with a concomitant antithrombotic medication vs 0.6% with no antithrombotic and 2.5% in patients taking LEQEMBI with an anticoagulant alone or with antiplatelet medication such as aspirin vs none in patients receiving placebo.

Fatal cerebral hemorrhage has occurred in 1 patient taking an anti-amyloid monoclonal antibody in the setting of focal neurologic symptoms of ARIA and the use of a thrombolytic agent.

Additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with LEQEMBI.

Caution should be exercised when considering the use of LEQEMBI in patients with factors that indicate an increased risk for ICH and, in particular, patients who need to be on anticoagulant therapy or patients with findings on MRI that are suggestive of CAA.

Radiographic Severity With LEQEMBI

Most ARIA-E radiographic events occurred within the first 7 doses, although ARIA can occur at any time, and patients can have >1 episode. Maximum radiographic severity of ARIA-E with LEQEMBI was mild in 4%, moderate in 7%, and severe in 1% of patients. Resolution of ARIA-E on MRI occurred in 52% of patients by 12 weeks, 81% by 17 weeks, and 100% overall after detection. Maximum radiographic severity of ARIA-H microhemorrhage with LEQEMBI was mild in 9%, moderate in 2%, and severe in 3% of patients; superficial siderosis was mild in 4%, moderate in 1%, and severe in 0.4% of patients. With LEQEMBI, the rate of severe radiographic ARIA-E was highest in ApoE ε4 homozygotes (5%) vs heterozygotes (0.4%) or noncarriers (0%). With LEQEMBI, the rate of severe radiographic ARIA-H was highest in ApoE ε4 homozygotes (13.5%) vs heterozygotes (2.1%) or noncarriers (1.1%).

Monitoring and Dose Management Guidelines

Baseline brain MRI and periodic monitoring with MRI are recommended. Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment. Depending on ARIA-E and ARIA-H clinical symptoms and radiographic severity, use clinical judgment when considering whether to continue dosing or to temporarily or permanently discontinue LEQEMBI. If a patient experiences ARIA symptoms, clinical evaluation should be performed, including MRI if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment.

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred with LEQEMBI. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction and initiate appropriate therapy.

INFUSION-RELATED REACTIONS (IRRs)

IRRs were observed—LEQEMBI: 26%; placebo: 7% — and most cases with LEQEMBI (75%) occurred with the first infusion. IRRs were mostly mild (69%) or moderate (28%). Symptoms included fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain), nausea, vomiting, hypotension, hypertension, and oxygen desaturation.

In the event of an IRR, the infusion rate may be reduced or discontinued, and appropriate therapy initiated as clinically indicated. Consider prophylactic treatment prior to future infusions with antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs, or corticosteroids.

ADVERSE REACTIONS

The most common adverse reactions reported in ≥5% with LEQEMBI and ≥2% higher than placebo were IRRs (LEQEMBI: 26%; placebo: 7%), ARIA-H (LEQEMBI: 14%; placebo: 8%), ARIA-E (LEQEMBI: 13%; placebo: 2%), headache (LEQEMBI: 11%; placebo: 8%), superficial siderosis of central nervous system (LEQEMBI: 6%; placebo: 3%), rash (LEQEMBI: 6%; placebo: 4%), and nausea/vomiting (LEQEMBI: 6%; placebo: 4%).

Please see full Prescribing Information for LEQEMBI, including Boxed WARNING.

This program was sponsored by Eisai, Inc., and Biogen. If you missed any part of this discussion, visit ReachMD.com. This is ReachMD. Be part of the knowledge.