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A Look at Lecanemab: The Latest Breakthrough in Alzheimer's Treatment

Dr. Wilner:
Having loved ones living with Alzheimer's disease can be difficult. According to the Alzheimer's Association, the disease affects at least 6.5 million Americans. Alzheimer's disease is the most common form of dementia, and symptoms become more severe over time. It is the leading cause of disability and poor health in older adults. Although there is no cure, a new medication, lecanemab, recently received accelerated approval by the US Food and Drug Administration. So where does lecanemab fit in the treatment of Alzheimer's disease?

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner. And joining me to talk about the recent FDA approval of lecanemab is fellow ReachMD host Dr. David Weisman. He's the Director of Clinical Research at Abington Neurological Associates and has devoted his research career to developing disease-modifying drugs for Alzheimer's disease.

Welcome, Dr. Weisman.

Dr. Weisman:
Thank you so much.

Dr. Wilner:
Before we jump into our topic, Dr. Weisman, please tell us which therapies are currently available for patients with Alzheimer's disease.

Dr. Weisman:
It's pretty much a therapeutic desert out there. For early Alzheimer's disease, we have medications that are symptomatic, and that's been the focus for many years, symptomatic medications like donepezil or all the acetylcholinesterase inhibitors that increase memory. We have medications that soothe neuropsychiatric problems which get worse and worse as the disease progresses. And then in later disease, there's the approval of memantine, which is really only approved and appropriate for later-stage disease. All of these are symptomatic medications, so that's been the landscape until very recently.

Dr. Wilner:
So is lecanemab a disease-modifying agent, or is it a symptomatic agent?

Dr. Weisman:
It is disease modifying. Alzheimer's disease is due to amyloid. Amyloid is really complicated. There are many, many types of amyloid, but what's been shown by lecanemab and a previous accelerate approval, aducanumab, is it gets rid of amyloid out of the brain. Without amyloid people tend to progress slower, so by any definition it's disease modifying.

Dr. Wilner:

Okay. So now you mentioned aducanumab. What's the difference between the two?

Dr. Weisman:
Aducanumab has become a very polarizing force in the community. Aducanumab had one positive trial and one negative trial. Both of the trials showed robust elimination of amyloid on PET scan, and biomarkers were similar, but unfortunately, with aducanumab, the entire study was judged to be futile, which is a statistical analysis where we're trying to predict the future, and they didn't predict the future properly because when the trial was said and done, one trial was positive and one trial was negative. The FDA took that data, and they gave it accelerated approval based on the surrogate biomarker of amyloid removal.

Since then two amyloid drugs have been positive: donanemab and now lecanemab, and they are all similar. They have overlapping mechanisms. They're all antibodies that get a target and get rid of amyloid out of the brain. They have been shown to get rid of PET amyloid. And so far that looks like that's associated with slower disease progress over a trial that's about a year and a half in a disease that's about one to two decades long. So the short answer is lecanemab has a lot of overlap with aducanumab. The main difference for any clinician is aducanumab has very high rates of this thing called ARIA, which is amyloid-related imaging abnormality, and it goes by the acronym ARIA, and basically, it's a brain swelling. It's increased vascular permeability. Aducanumab is really good at doing that and making vessels more permeable. They leak fluid into the brain. We pick that up on MRI. Sometimes it causes symptoms. Lecanemab, with its overlapping mechanism, certainly causes ARIA but much less of it.

Dr. Wilner:
I can see a scenario if you had, an older person who has been diagnosed with early Alzheimer's and is still quite functional who wants to remain functional as long as possible that this drug might fit in. On the other hand, if you have someone with Alzheimer's disease who already is impaired to the point where they're having trouble with their activities of daily living, would this drug be appropriate for that second group?

Dr. Weisman:
Generally, no. A normal person with a little bit of memory loss, that's kind of the perfect person for this drug. Those are the people who got into this trial. They had pretty deep amnesia, but they were very functional, mostly MCI and very early Alzheimer's disease. As the disease gets worse, there is more tradeoff, right? About the same risk but maybe no benefit. And at some point, it's just all risk and no benefit, and where that point is, I mean, frankly, we're going to have to figure that out. I mean, there are many people with this multifaceted disease, maybe cognitively they're not so good, but functionally they are good. I'm not certain I would close the door entirely to such a case, but in general, the later you are the less you can possibly benefit from this.

Dr. Wilner:
Are there any specific populations of people with Alzheimer's disease who should not get lecanemab?

Dr. Weisman:
There are two main categories of people who the risk is higher. The first is people who have genetically APOE 44. Homozygote A4 people are extremely high risk of getting Alzheimer's disease because the gene codes for a protein that can't get rid of amyloid, so the amyloid builds up in the brain. It also builds up into their vasculature, and it's that vascular amyloid that creates the vascular permeability, and that creates the brain swelling. And what we see with lecanemab is that people who are APOE 44 have about a one in three chance of getting the brain edema. Now that's down to about 5 percent for people who are noncarriers.

The second category of folks who tread with caution are people on anticoagulation. Full anticoagulation is not a contraindication to getting lecanemab. People got anticoagulation within the trial of lecanemab, but there is an increased risk of ARIA-E during the trial. Basically, messing with amyloid creating increased vascular permeability, having anticoagulation also on board was not so good. There were a couple of deaths, and they have all been tied with anticoagulation, and in one case with thrombolysis. Somebody had a left MCA occlusion that was not mechanically amenable and got IV tPA and had a catastrophic outcome.

Dr. Wilner:

For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and I'm speaking with Dr. David Weisman about the FDA-approved drug for Alzheimer's: lecanemab.

Okay. So, Dr. Weisman, let's get to the clinic. I'm going to clinic tomorrow. I have a patient, they come in. I've diagnosed them before with Alzheimer's. Things are not getting better, but they're managing. I think this patient might be a good candidate for this drug. Can I write a script?

Dr. Weisman:
Yes. The process by which you can do that is, first of all, we have to confirm that they have amyloid because if they don't have the target amyloid, then there's no sense going after it. Right? No target, hold your fire. Have amyloid, then we're good to go. Currently, we cannot get a PET scan because Medicare doesn't pay for them, but you can get CSF, so what I've been doing is I've been sending these people to fluoroscopy because it's a little bit of an easier sell to them to talk about how we're going to do it under x-ray, and it's like shooting fish in a barrel, and it's a very thin needle, and they are very comforted by that, and there's no urgency here. We can set them up with pain management or interventional radiology and get it under fluoroscopy, or you could do it bedside. I've done it in my clinic. You need amyloid confirmation, and the way to do it currently is CSF. LabCorp has a very easy, very intuitive test. It's a ratio of 42 and 40, but basically, 42 is very sticky. And we're all making this amyloid, but if it sticks into the brain, it doesn't get out into the CSF, and that's what we're looking for is aggregated amyloid when we're doing the LP. So we have low amyloid in the CSF, and that is the pathophysiology of Alzheimer's disease. We're measuring aggregated species in the brain.

Assuming they have the biomarkers, then yes, you can write a script. The problem is right now Medicare does not cover it.

Dr. Wilner:
What kind of follow-up is required?

Dr. Weisman:
We have to get an MRI within about a year-ish. The MRI, to get into it, you have to look for ARIA-H. We talked about amyloid-related imaging abnormality edema, but there is ARIA-H where the vessels become so fragile that they create little micro bleeds and even macro hemorrhages. A lot of the macro hemorrhages that we see in the ER are due to cerebral amyloid angiopathy.

Where does amyloid come from? It comes from the brain. And all these people have Alzheimer's by pathology, so we have to make certain that it's safe to give it to them, and then we have to monitor them for the brain edema, and you just have to be diligent about that. So this medication clearly is not for everybody. They have got to get CSF. They have to get an infusion. Then they have to get MRIs serially.

Dr. Wilner:
Okay. Well let's step back for a moment. And from your vantage point as a clinical researcher, would you consider this a breakthrough for Alzheimer's disease in terms of treatment?

Dr. Weisman:
You know, yes. I mean, obviously. We've had nothing for this disease for my entire career. I was a medical student, and I was told that it was impossible to get rid of amyloid. It's like rebar in concrete. I mean, to actually see amyloid melting away on a PET scan is magical. To imagine that we now have the ability to slow down the progression of this fatal and dreaded disease is unbelievable. And right now, a patient who has paid into Medicare all of their life, to not get this thing covered by Medicare, I mean, it's an abomination. It's ridiculous.

Dr. Wilner:
Before we close, Dr. Weisman, are there any final thoughts you would like to share with our audience today?

Dr. Weisman:
Look at the data. The data solves all the arguments. There are a lot of anti-amyloid people, and if you were dimly aware of all the anti-amyloid trials that failed, it's very easy to be biased. Failure, failure, failure, failure. But what you may not have seen during all those years we have been working on this is that every failure gave us a learning opportunity to build on. We really started standing on the shoulders of other people and failed trials where one failure has given us data so that we can get to a success. And we're not done. This medication is not a drug anymore. It's now an approved medication. Slows things down 30 percent. I mean, there's 70 percent to go. And neurologists are going to have to focus on how to talk about a 30 percent slowing. We're going to have to talk about risk because a lot of patients and their caregivers are very risk-tolerant for this disease, especially if they have seen other people go through the disease, and we're going to have to be able to figure out what their risk is. And there are ways of doing that. So we're basically going to have to turn into genetic counselors and really listen to the patient as they discuss their risk tolerance with us. And this is the beginning of turning this field into oncology with all the successes there. It's not the end. Further trials will get at that rest of the 70 percent, and fingers crossed this will be a stable disease one day.

Dr. Wilner:
Well, Dr. Weisman, that is very encouraging, and I want to thank you for this insightful look at a new therapy for patients with Alzheimer's disease. Dr. Weisman, thanks for sharing your thoughts.

Dr. Weisman:
Thank you. Thanks for having me.

Dr. Wilner:
For ReachMD, I'm Dr. Andrew Wilner. To access this and other episodes in our series, visit ReachMD.com/NeuroFrontiers where you can Be Part of the Knowledge. Thanks for listening.