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What Are the Data Behind ATT?

Announcer:
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Dr. Isaacson:
Welcome to the Frontline of Alzheimer's Care, where we provide you with quick answers to burning questions from real clinicians about amyloid-targeting therapies in Alzheimer's disease. I'm Dr. Richard Isaacson and here with me today to help answer these questions are doctors Gayatri Devi and Pierre Tariot. Here's a question from Dr. Gary Grove.

Dr. Grove:
Are there any significant differences between lecanemab and donanemab in terms of efficacy and safety?

Dr Isaacson:
Dr. Tariot, what do you think? What are some key points regarding this comparison?

Dr. Tariot:
Yeah, thank you and it's a great question. The context is this - earlier studies with anti-amyloid antibodies showed that you could actually remove pathological amyloid deposits from the living human brains of people with Alzheimer's disease, which was an amazing advance. And then the question became, is that associated with clinical benefit? So where we're at is that three different agents, aducanumab, lecanemab, and donanemab have been studied in generally similar ways. People had to have MCI or mild dementia due to Alzheimer's disease, which is defined as elevated brain amyloid based on PET scan or CSF testing.

They all remove pathological amyloid deposits from the living human brain. The studies have a lot - the different agents have a lot in common, but there's some key differences.

Aducanumab was the first one out of the gate, two large phase 3 programs. The drug is titrated over 6 months, monthly infusions. And the trial program was stopped because of a futility analysis suggesting lack of benefit, but it turned out one of the trials was positive, one of the trials was not so the FDA granted what's called accelerated approval, it can be used, but this isn't traditional approval, another study needs to be done. There was about 22% less slowing over 18 months on drug versus placebo.

Lecanemab, the second one on the table, given as a once a month infusion until amyloid is cleared from the brain, which is a different approach. Lecanemab again, similar patient population, people with elevated brain amyloid with mild cognitive impairment or mild dementia, lecanemab, no titration, given every 2 weeks, 27% less slowing over 18 months.

Donanemab, similar patient population with one notable exception in that program. Patients also had to have a certain level of elevated pathological tau protein as measured by PET scan. The primary outcome was in people with, quote, low to medium tau. The secondary was that group combined with the high tau 35% less slowing on donanemab at a year and a half compared to placebo. So that's kind of the efficacy top line. Safety we'll drill down on again a little bit later, but the biggest adverse event was something called amyloid-related

imaging abnormality-edema, in plain English, kind of like vasogenic edema.

Dr. Isaacson:
That was great. That was as concise as one can be for quite a question. Dr. Devi, you know, you've had a ton of clinical experience here. What are some of your thoughts?

Dr. Devi:
All three drugs clear plaque in the brain. All three drugs also reduce tau in the brain. However, aducanumab, which is the first conditionally approved drug, and donanemab, which may soon get approval cause a higher level of amyloid-related imaging abnormalities, including brain edema and brain hemorrhage in about 43% in patients who have a copy of an E4 allele, less than people who have no copies of the APOE4 allele. Lecanemab has a 22 to 25% risk of those side effects.

Dr. Isaacson:
Great. Well, very important points and appreciate that perspective very much. Well, I also wanted to thank Dr. Grove, because that was a great question. And for our viewers, check out our other episodes for more questions on the ins and outs of amyloid-targeting therapy. Thanks so much for joining us today.

Announcer:
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