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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Which Amyloid-Targeting Therapy is Best?

Announcer:
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Dr. Isaacson:
Welcome to the Frontline of Alzheimer's care, where we answer real questions from real clinicians about amyloid-targeting therapies in Alzheimer's disease. I'm Dr. Richard Isaacson, and joining me today to answer these questions are doctors Gayatri Devi and Pierre Tariot.

Our first question is from Dr. Derek Chong.

Dr. Chong:
Aducanumab, lecanemab, and donanemab, they are all of the amyloid-targeting therapies that I believe are available or soon to be available. I'm wondering if you think that they're all going to be pretty similar in, or do you think that one will be better for a specific type of patient versus another one? Or you think that one is just going to be better than the rest for basically all patients?

Dr. Isaacson:
Well, that's a really important question. And as the era of precision medicine in Alzheimer's disease develops I hope that we can answer these questions with a lot more detail than we can answer them today.

That being said, there was a head-to-head study with donanemab versus aducanumab. It was 148 patients. And now this was a study that compared amyloid clearance in the patient groups, and that study showed a fair amount greater amyloid clearance in the donanemab group, and that was at 6 months, but it did not report out any efficacy measures. So we're really unclear about that.

So what I would say is as we continue to learn, and as the data continues to pour in, we'll be able to answer this question quite a bit better

Dr. Tariot:
Yeah. Just a couple of additional thoughts, Richard. The evidence seems to be mounting that treating earlier in the course of illness is probably going to be more effective. There are brand new data just presented in late 23 on this point with donanemab, including in persons with a very low tau level. So that's interesting. So that trend is emerging.

I think another point worth stressing is the donanemab approach was to treat until amyloid was cleared according to PET scan. That's different from the other agents and raises the question of, if it's approved by FDA, what will the language be around duration of therapy, follow up beta amyloid testing, and so forth? Donanemab also had a high rate of what are called anti-therapeutic antibodies in comparison to the other agents, and that is being dealt with with a follow-on compound that's going to presumably lack that attribute. Maybe it's the reason that there might be slightly higher infusion-related reactions with donanemab.

And lastly all three agents are being developed as subcutaneous formulations, which could actually be quite a game changer.

Dr. Isaacson:
Yeah, there was just some recent data, the Clinical Trials in Alzheimer's Meeting about the subcutaneous efficacy and safety of lecanemab that was very interesting, some of the - a little bit more safety potential issues with the at-home treatments. But again this is just one drug and one study and maybe needs to be a titrated dose and these again, very early days in terms of understanding the differential effects of these agents.

But Dr. Devi, you have a ton of experience here. You're one of the earliest adopters and the most experienced clinicians that I know with these drugs. What is some of your perspective here?

Dr. Devi:
When we're treating patients with monoclonal antibodies targeting beta amyloid, you have to be cognizant of the fact that each of these monoclonal antibodies, whether it's aducanumab, lecanemab, or donanemab, they target different epitopes of the amyloid plaque or the protofibril or other component of the plaque. Therefore, it may be that one patient may have better response to one of the monoclonal antibodies, depending on the kind of epitope that's best cleared with that patient.

So what I've done in my practice is when patients did not do well, when there wasn't discernible plaque clearance with aducanumab, the first approved drug, then I switch them to lecanemab, which is the second approved drug. And truth be told, when the third drug comes out, donanemab hopefully in early 2024, I'd probably go ahead and scan patients, and if they still continue to have plaque, I might switch them to the third monoclonal antibody just to see if they respond better to it in terms of plaque clearance.

In terms of clinical efficacy, all the three drugs are essentially about the same.

Dr. Isaacson:
Yeah, these are really, really great, important points. And, you know, I feel like as we continue to learn and collect data, maybe one day we will have more clarity which is maybe better for men versus women, or people with two copies of the APOE4 variant are at higher risk from one drug, so maybe we should use a different drug, and that drug may have better or neutral efficacy outcomes in comparison. So I think as the data you know, or our universal data increases, we're going to be much better positioned to answer this question. And also make more well-informed decisions.

I think, also, aside from, you know, our PET scans and our MRIs and our spinal taps that we really need to follow over time for both safety and efficacy reasons. You know, the blood-based biomarkers, there's really a whole new era. In the next year or 2 there's just going to be an explosion of the use of these biomarkers. And hopefully, we can use simple blood test to truly understand in real time the pathological targeting and target engagement of these drugs.

So, thank you, Dr. Chong. Thank you, Pierre, Gayatri that was a very thought-provoking question. For our viewers, listen to our other episodes for more great questions about the clinical use of amyloid-targeting therapies. Thanks so much for listening.

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