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Comparative Efficacy: SubQ vs. Intravenous DMTs in Alzheimer's Disease

Announcer:
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Dr Sabbagh:
This is CME on ReachMD and I'm Dr. Marwan Noel Sabbagh. Today we're going to discuss comparative efficacy, subcutaneous versus intravenous disease modifying therapies in Alzheimer's disease.

We understand a lot, and if you look at donanemab, aducanumab, and lecanemab, these are second-generation monoclonal antibodies. We understand that certain species of amyloid matters, so targeting previous generation monoclonals that targeted monomers didn't have any efficacy signals and so we understand that the toxic species, which includes oligomers, protofibrils and fibrils, and the plaque, might be the appropriate species to target.

Lecanemab targets the protofibrils, aducanumab the protofibrils and oligomers, donanemab the pyroglutamate epitope and fibrils. So, the point is, is that the species of amyloid matters, and that's why we're probably seeing better efficacy signals among the reasons in the new generation of monoclonal antibodies.

So let's turn our attention to lecanemab, which was approved in early 2023. When you look at the prespecified primary endpoint of the CDR, clinical dementia rating scale, some of the boxes, this is a large study, about 1,800 people, about almost 900, we see that the patients in the treated group, the lecanemab group, slowed the rate decline by 27% compared to the placebo group. And remember, both were allowed to be on standard of care, meaning memantine, donepezil, etc. So, this is lecanemab plus standard care versus placebo plus standard care slowed the rate declined 27%. When we looked at their activities of daily living, it slowed the rate of decline up to 40%, and so we know that it has robust slowing in the rate of functional impairment.

Now people are looking itno the future of the idea that, could we give lecanemab subcutaneously as opposed to intravenously. And when you look at the PK of intravenous versus subcutaneous, very, very similar PKs, and so that could make the argument that the concentration serum-wise is very similar and could mean that subcutaneous is an option. This is still under development, we don't know when this will be approved or available, but this might be an option in the future.

When we look at another monoclonal antibody, donanemab, we know that the TRAILBLAZER-ALZ 1 study slowed the rate of decline 32% of donanemab versus placebo on the composite measure, the iADRS. And when they did their Phase 3 trial, the TRAILBLAZER-ALZ 2 trial, roughly about seventeen to eighteen hundred participants, they also showed the rate decline about 30% slowing both on the composite measure that iADRS, and on the CDR, the clinical dementia rating scale, in both measures, depending on what population we're looking at. All of them showed that it met its prespecified endpoint.

I want to point this slide out to you because it's very, very important that you understand that if you look at patient C, you see that in placebo group, there was no removal of amyloid. That's the red on the sagittal cut. But when you look at patient B, there is complete

removal of amyloid on the patient B. So, that suggests that we can remove amyloid and we can do it very, very well below 11 centiloids.

Now, you also need to understand that it had other things that are relevant here, right? Almost 50% of patients had no functional cognitive decline after a year, that it has stabilization on activities of daily living, up to 40% of slowing, that they delayed progression to the next level on the CDR up to 40%, that amyloid was cleared out of the brain as early as 6 months, and that 71% of patients actually had no amyloid in the brain by 12 months, that we understand that there is a risk of ARIA up to 24% in patients with ARIA-E in the treated group, and ARIA-H about 30%.

People ask me all the time, why would we treat amyloid hypothesis, it's not relevant, and I say to you that maybe amyloid has not historically correlated with clinical progression, but Tau does. And so maybe, the effect might be driven not directly by the removal of amyloid, but by the fact that other biomarkers, such as Tau, go down. So, when you remove amyloid, as you see on the left-hand side, you see Tau levels start to fall as well on the right-hand side. So, maybe the effect is driven by the fact that removal of amyloid drives the lowering of other biomarkers such as Tau.

So, in summary, we know that the clinical efficacy signal of monoclonals has been demonstrated, that in a dose-dependent manner, the more amyloid removed, the more slowing in the rate of decline now, with lecanemab and donanemab, and it might be driven by secondary biomarkers.

Thank you for listening.

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