Donanemab: A trailblazer for Alzheimer's disease treatment?

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A recent study published in the journal *JAMA* evaluated the efficacy and side effects of donanemab. They aimed to use this antibody to clear brain amyloid plaque in randomized participants with early symptomatic Alzheimer disease (AD) with low/medium or high tau pathology.

Study: Donanemab in Early Symptomatic Alzheimer Disease The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. Image Credit: perfectlab/Shutterstock.com

Background

Early-stage AD involves the buildup of beta-amyloid, which results in neurofibrillary tangles made of tau protein and other distinctive brain alterations collectively known as the amyloid cascade.

However, not many trials have shown a significant slowdown in disease progression. Only limited clinical trials have shown promising results in amyloid-targeting treatment options, such as auranumab, lecanemab, and donanemab.

In this study, researchers designed and investigated the use of donanemab, a monoclonal immunoglobulin G1 antibody, which targets an insoluble, mutated, and N-terminally shortened form of β-amyloid found in brain amyloid plaques.

The TRAILBLAZER-Alzheimer (ALZ) trial, comparing donanemab to placebo, met the primary outcome, but imaging abnormalities and infusion-related responses were identified as undesirable outcomes.

To build on this, the TRAILBLAZER-ALZ 2 trial, a global phase 3 randomized clinical trial, analyzed donanemab efficacy and adverse events in a combined population with low/ medium and combined high tau pathology, a population considered more challenging to treat due to advanced disease. These findings confirm and expand the findings from TRAILBLAZER-ALZ.

About the study

The study conducted a randomized, double-blind, parallel, multicenter, placebo-controlled trial involving 277 locations across 8 countries. Participants of the 76-week trial ranged in age from 60 to 85 and had early-stage AD symptoms. Participants were considered eligible if they had a mini-mental state examination score of 20 to 28 and had undergone positron emission tomography (PET) and tau pathology analysis. To comprehend differences in illness progression, treatment outcomes, or adverse events, demographic data was gathered. Every four weeks for up to 72 weeks, participants were randomized to receive intravenous doses of donanemab or a placebo.

The study examined amyloid-related imaging abnormalities with scheduled and unscheduled MRIs and evaluated 76 weeks of efficacy. Participants with abnormalities were rechecked every 4 to 6 weeks to see if they had improved or stabilized. Microhemorrhages, hemosiderin deposits, and edema/effusion normalized while infusions were postponed.

Phase 2 of the trial's initial phase tested the clinical dementia rating scale sum of boxes (CDR-SB) with 500 participants as the primary outcome. It was converted to a phase 3 experiment in February 2021, expanding on the results of the TRAILBLAZER-ALZ trial.

No unblinded data analysis was performed. The study changed its sample size and power calculations in light of the trial's key conclusions. Each sample was fitted to the natural cubic spline model with two degrees of freedom (NCS2), with the power dependent on the low/medium tau population.

The NCS model had above 95% power with a sample size of 1000 randomized individuals and a 30% discontinuation rate. For statistical analysis, the study used Statistical Analysis System (SAS) version 9.4 and, for time-based progression analyses, R Project version 4.3.0. To calculate the percentage of clinical illness progression halted, analysis of covariance was utilized.

Results

The study results showed that donanemab had clinically substantial advantages, including a 38.6% risk reduction of disease progression and 4.4 to 7.5 months saved over the course of the 18-month research. Donanemab effectively slowed the advancement of AD in populations with low/medium and mixed levels of tau.

Furthermore, compared to 29% of those getting placebo, 47% of those receiving donanemab exhibited no change in CDR-SB at one year. By one year, cerebral amyloid plaque had significantly decreased in 52% of low/medium tau participants, with 80% achieving amyloid clearance at 76 weeks.

The use of limited-duration dosage was put into place to reduce stress, cost, and the possibility of receiving unnecessary treatments. Early, significant abnormalities are detected by P-tau blood tests and brain amyloid PET scans, suggesting the possibility of clinical surveillance.

Donanemab and other amyloid-lowering medications are associated with amyloid-related imaging abnormalities. Usually asymptomatic, these anomalies disappear within 10 weeks. They can range in severity from seizures to more minor symptoms such as headaches or confusion.

These occurrences occasionally have the potential to be fatal and life-threatening. In the donanemab therapy group, 1.6% of patients had major side effects that required supportive care or hospitalization.

It has been speculated that early AD treatment has more clinically significant

results. Except for CDR-SB, post hoc analysis among people with high levels of tau revealed no significant changes in primary or secondary outcomes across donanemab-treated and placebo-treated subjects. For limiting risks and maximizing benefits, additional investigation of risks associated with serious and fatal abnormalities is necessary.

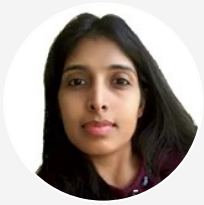
Conclusion

The general consensus states that treating AD at an earlier stage is more likely to produce clinically significant results. This study showed that donanemab markedly slowed clinical progression at 76 weeks in participants with low/moderate tau and in the combined low/medium and high tau pathology population.

Thus, this study provides support for the hypothesis that amyloid-lowering therapies may be more effective when initiated at an earlier stage of AD.

Journal reference:

- Sims JR, Zimmer JA, Evans CD, et al. (2023). *JAMA*. Donanemab in early symptomatic Alzheimer disease the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. **doi:** 10.1001/jama.2023.13239. https://jamanetwork.com/journals/jama/fullarticle/2807533



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Susha has a Bachelor of Science (B.Sc.) degree in Chemistry and Master of Science (M.Sc) degree in Biochemistry from the University of Calicut, India. She always had a keen interest in medical and health science. As part of her masters degree, she specialized in Biochemistry, with an emphasis on Microbiology, Physiology, Biotechnology, and Nutrition. In her spare time, she loves to cook up a storm in the kitchen with her super-messy baking experiments.