Title: Donanemab: A New Promising Treatment for Alzheimer's Disease?

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Key highlights:

- Based on CLARITY AD (NCT03887455) and TRAILBLAZER-ALZ 2 (NCT04437511) clinical trials, Donanemab and Lecanemab, both novel anti-amyloid immunoglobulin treatments, have shown significant efficacy in reducing amyloid beta plaques, a hallmark of Alzheimer's disease (AD). However, Donanemab's newly released clinical data possibly demonstrates a more substantial reduction of amyloid burden and a more significant slowing of cognitive decline associated with AD.
- Although Donanemab demonstrates efficacy in slowing disease progression, it may be associated with high rates of adverse events, notably infusion-related reactions, and Amyloid-Related Imaging Abnormalities (ARIA).
- Both Donanemab and Lecanemab reported an increased risk of Amyloid-Related Imaging Abnormalities (ARIA) in patients, particularly APOE4 carriers.
- The demographic characteristics of participants varied between the two phase-III clinical trials, with the Lecanemab trial being more globally diverse. This might influence the generalizability of results and underscores the need for more inclusive and diverse clinical trials in AD.
- Head-to-head trials are warranted to compare Donanemab to the FDA-approved Lecanemab, in order to draw stronger conclusions related to the efficacy, tolerability, and safety of each drug.

Text

The past couple years have witnessed major advances with the development and approval of anti-amyloid disease-modifying therapies for Alzheimer's disease (AD), starting with Aducanumab (Eisai/Biogen), which was the first monoclonal antibody approved by the Food and Drug administration (FDA) agency under the accelerated approval pathway for mild cognitive impairment (MCI) and mild AD in June 2021. This drug was met with skepticism by many experts due to methodological flaws and failure to consistently demostrate a relationship between removing the amyloid plaques and slowing cognitive decline in its two seminal phase III clinical trials. Two years later, Lecanemab another monoclonal antibody manufactured by the same companies (Eisai/Biogen) received full/traditional FDA-approval in July 2023, in the same patient population with MCI and mild AD. Unlike Aducanumab, Lecanemab will be financially covered by the Centers for Medicare & Medicaid Services (CMS) in the United States, to promote availability to eligible patients (1). During the same month, breakthrough positive data from a phase III clinical trial with a third monoclonal antibody donanemab (Eli Lilly) was released during the Alzheimer's Association international conference (AAIC), which brings greater hope and therapeutic options to patients struggling with this debilitating disease (2).

Figure 1 shows the pathological targets of these three anti-amyloid immunoglobulins.

Donanemab (LY3002813, Eli Lilly) is an IgG1 monoclonal antibody, administered through monthly intravenous injections, that targets cortical insoluble β-amyloid (Aβp3-42), a pyroglutamate form of Amyloid-β (Aβ) exclusively found in the plaques.

First, a 72-week phase II trial with this compound, the TRAILBLAZER-ALZ, enrolled 257 patients aged 60 to 85 years who had MCI and mild AD (early AD), with evidence of positive tau and amyloid deposits on flortaucipir and florbetapir PET scans. Subjects were required to have a quantitative tau load below a specific upper threshold, to exclude those with more severe illness that may not respond to anti-amyloid agents. One hundred and thirty-one subjects had received donanemab IV infusions every 4 weeks, at the dose of 700 mg (~10 mg/kg) for the first 3 infusions, increased thereafter to 1400 mg (3). The primary outcome was the change from baseline to 76 weeks in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS). It is a composite score that combines the ADAS-Cog 13 and the Alzheimer's Disease Cooperative Study–Instrumental Activities of

Daily Living Inventory (ADCS-iADL). Secondary outcomes included among others the change in the amyloid and tau burden as assessed by florbetapir and flortaucipir PET scans. There was a significant change from baseline in the iADRS score at 76 weeks (−6.86 in the donanemab group and −10.06 in the placebo group; difference of 3.20; 95% confidence interval [CI], 0.12 to 6.27; P = 0.04). Additionally, this product significantly decreased brain amyloid burden. The percentage of participants in the experimental group who switched from being amyloid positive to an amyloid negative status were 40.0%, 59.8%, and 67.8%, at 24, 52, and 76 weeks, respectively. There was no effect on the global tau brain load. The drug was found to be safe and well-tolerated.

ARIA refers to changes in brain imaging associated with the use of amyloid-targeting therapies in Alzheimer's disease, which are typically classified into two types: ARIA-E (edema or effusion) and ARIA-H (hemosiderin deposits, indicative of microbleeds).The incidence of ARIA-E was significantly higher in the donanemab group than in the placebo group (26.7% vs. 0.8%; $p < 0.001$; 6.1% were symptomatic). The incidence of ARIA-H was comparable in both groups (8.4% in the treatment group, compared to 3.2% in the placebo group; $p = 0.11$). Discontinuation rates due to adverse events was significantly higher in the treatment group compared to placebo (15.3% versus 4.8%; $p = 0.007$).

The positive data from its phase III clinical trial TRAILBLAZER-ALZ 2 (4) were published in July 2023, paving the way for Eli Lilly to apply for FDA approval of the drug in individuals with early AD. The TRAILBLAZER-ALZ 2 trial involved 1736 patients, from 277 medical sites in 8 countries, aged between 60 and 85 (mean age: 73.0), divided into two populations depending on tau burden (low/medium tau pathology and combined low/medium and high tau pathology). 860 participants received Donanemab (700 mg for the first 3 doses and 1400 mg thereafter) and 876 received placebo, each administered intravenously every 4 weeks for up to 72 weeks. Eligibility criteria included having a baseline Mini-mental state examination (MMSE) score of 20 to 28, amyloid pathology (≥37 Centiloids assessed through F-florbetapir or F-floberaben PET). Tau pathology was assessed by F-flortaucipir PET. A post-hoc analysis was done evaluating Donanemab strictly in participants with high tau pathology (n = 552; 31.8%).

With regards to the amyloid burden, Donanemab has shown significant efficacy in reducing plaques. In low/medium tau and mixed tau populations, Donanemab treatment resulted in an impressive 80% and 76% clearance rate (< 24.1 centiloids)

respectively at 76 weeks. Particularly, the mean change from baseline in the low/medium tau group was -88.0 Centiloids, while in the mixed tau group, it was -87.0 Centiloids.

In terms of impact on cognition, Donanemab demonstrated a 35.1% slowing of disease progression in the low/medium tau group, and a 22.3% slowing in the mixed population, as measured by the change in the iADRS scores, over a 76-week period. This exceeded the threshold of 20%, suggesting a clinically meaningful benefit in treating early-stage Alzheimer's disease.

This substantial reduction of amyloid beta plaques and subsequent slowing of Alzheimer's disease progression, supports the amyloid cascade hypothesis, which postulates that the accumulation of amyloid beta plaques leads to neurodegeneration and, consequently, cognitive decline in AD.

Positive findings were also noted on the secondary clinical outcomes, including the Clinical Dementia Rating Scale (CDR-SB), the ADAS-Cog13, the ADCS-iADL, and the MMSE. The low/medium tau group showed a 36.0% slowing in CDR-SB, 39.9% in ADCS-iADL, and 32.4% in ADAS-Cog13, while the mixed tau population demonstrated a 28.9% slowing in CDR-SB, 27.8% in ADCS-iADL, and 19.5% in ADAS-Cog13.

It is noteworthy that 47% of participants receiving Donanemab in the low/medium tau population had an unchanged CDR-SB score at one year from baseline, compared to only 29% of participants receiving placebo. This indicates that Donanemab might stabilize the disease in some patients, rather than slowing progression.

In comparison with Lecanemab that is administered intravenously every 2 weeks, Donanemab is administered every 4 weeks. Donanemab appears to yield a more substantial plaque reduction, suggesting it might be a more potent option for combating AD pathology. This efficacy comes with the trade-off of increased adverse events and safety concerns. When data is compared between the phase III clinical trial that led to the approval of Lecanemab (CLARITY-AD) (5) and the TRAILBLAZER-ALZ 2 trial, more patients discontinued Donanemab due to adverse events (13.1% vs 6.9% for Lecanemab), with infusion-related reactions being the most common followed by Amyloid-Related Imaging Abnormalities (ARIA). Both Lecanemab and Donanemab have been associated with these abnormalities. ARIA events are found to be particularly increased among APOE4 carriers.

Within 18 months, the incidence of ARIA-E in the Lecanemab group was 12.6%, compared to 24.0% in the Donanemab group. The incidence of symptomatic ARIA-E was relatively low in both groups, being 2.8% with Lecanemab and 6.1% with Donanemab. Also, ARIA-H was more common in the Donanemab group, with an incidence of 31.4% compared to 17.3% in the Lecanemab group. However, symptomatic ARIA-H was rare in both groups, occurring in 0.7% of patients.

In addition, the incidence of serious adverse events was 17.4% in the Donanemab trial compared to 14% in the Lecanemab trial.

In terms of safety, the mortality rates were low with both drugs reaching 0.7 and 1.9% for Lecanemab and Donanemab, respectively. 0.4% of deaths were attributed to donanemab, and were specifically linked to ARIA-E, compared to none of the deaths attributed to Lecanemab in CLARITY-AD.

In CLARITY AD, patients had a slightly higher baseline MMSE score (22–30) compared to those in the TRAILBLAZER-ALZ 2 trial (20-28). However, the baseline amyloid burden was greater in participants of the Donanemab trial (≈102.4 ± 34.7 vs 77.92 ± 44.84 centiloids). While CLARITY AD was more globally diverse (20% non-white participants), TRAILBLAZER-ALZ 2 was less so (9.5% non-white). Finally, both trials managed infusion-related reactions effectively.

Overall, while both drugs show evidence in slowing the progression of AD, and are generally tolerable and safe, the slightly higher efficacy of Donanemab comes with a minor increase in adverse events and safety concerns. This emphasizes the necessity for comprehensive prescription guidelines for these drugs in the future, which should incorporate APOE4 screening, accurate staging and classification of AD and diligent MRI monitoring. Furthermore, although baseline AD severity and treatment duration was similar in both phase 3 clinical trials, head-to-head trials comparing the two drugs in the same population and under the same conditions are needed to draw more accurate and reliable conclusions. On that note, data from the TRAILBLAZER-ALZ 4 that directly compared Donanemab to Aducanumab with respect to plaque clearance showed a significantly higher amyloid clearance and amyloid plaque reductions with Donanemab versus aducanumab at 6 months, on assessment of florbetapir F18 PET scans. Data incorporating comparing impact on cognition are also warranted (6).

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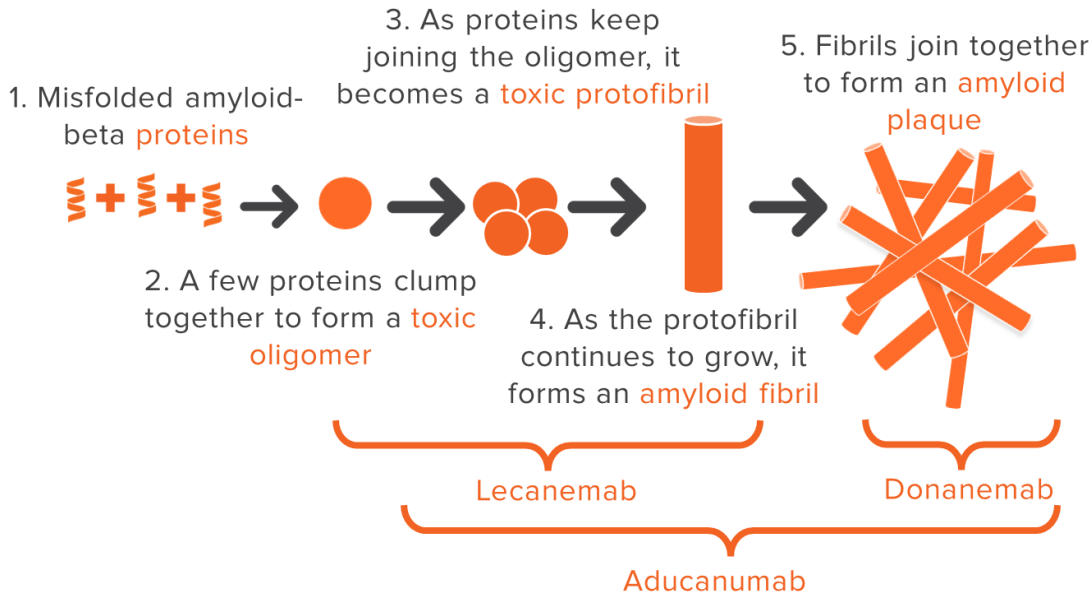

Figure 1. Pathological targets of the three anti-amyloid immunoglobulins: Aducanumab, Lecanemab and Donanemab.

Extracted from https://www.alzheimersresearchuk.org/blog/new-alzheimers-drug-donanemab-what-is-it-and-how-does-it-work/