COMMENTARY

Lilly's Donanemab, will it be the light at the end of the tunnel?

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Alzheimer's disease (AD), the most common form of dementia (approximately 80% of the disease), is characterized by gradual memory loss and cognitive disorder. Among the multiple factors that have now been identified to increase the incidence of AD, age is the largest risk factor. With the development of the global social economy and the acceleration of the aging process of the population, the morbidity and mortality of AD continue to increase, which is a great challenge for social development and global health care, and there is an urgent need to develop effective drugs that can reduce the incidence of AD and delay the disease process, otherwise, AD will cause intolerable losses to society and health care systems. At present, the deposition of extracellular amyloid-β (Aβ) plaques and intracellular hyperphosphorylated tau protein accumulation have been recognized as important hallmarks in the pathogenesis of AD. The amyloid cascade hypothesis of AD has proposed that deposition of amyloid-β (Aβ) peptide in the brain is a central event in disease pathology, this view has long been supported by neuropathological and human genetic evidence and has guided most of AD-related academic research and drug development over the past decades.

Just a few days ago, pharmaceutical company Eli Lilly announced the results of a phase III clinical trial of Donanemab, a monoclonal antibody drug for the treatment of AD, which showed that Donanemab significantly slowed the cognitive and functional decline in patients with early symptomatic AD, which is undoubtedly an exciting news for the field of research and treatment of AD. Donanemab, aka N3pG, is a humanized IgG1 monoclonal antibody developed from mouse mE8-IgG2a that targets a specific N-terminal epitope of amyloid-β that is present only in AD-related brain amyloid plaques, and this drug-targeted binding is able to rapidly clear amyloid plaques from the brain without off-target binding to other Aβ species. Donanemab works not just to prevent the deposition or increase of Aβ plaques, but also to target the deposited plaques simultaneously to eliminate the existing amyloid burden in the brain.

Also, as a specific clearance antibody for amyloid plaques in the brain, Aducanumab and Lecanemab were approved for marketing by the Food and Drug Administration (FDA) in June 2021 and January 2023, respectively, with accelerated approval. Aducanumab is currently available for the treatment of AD patients with mild cognitive impairment (MCI) or mild dementia, and it has been shown to clear amyloid plaques in the brain, but it has not shown a strong ability to slow memory loss or cognitive decline in patients in clinical trials, which has become a point of debate since Aducanumab was marketed,

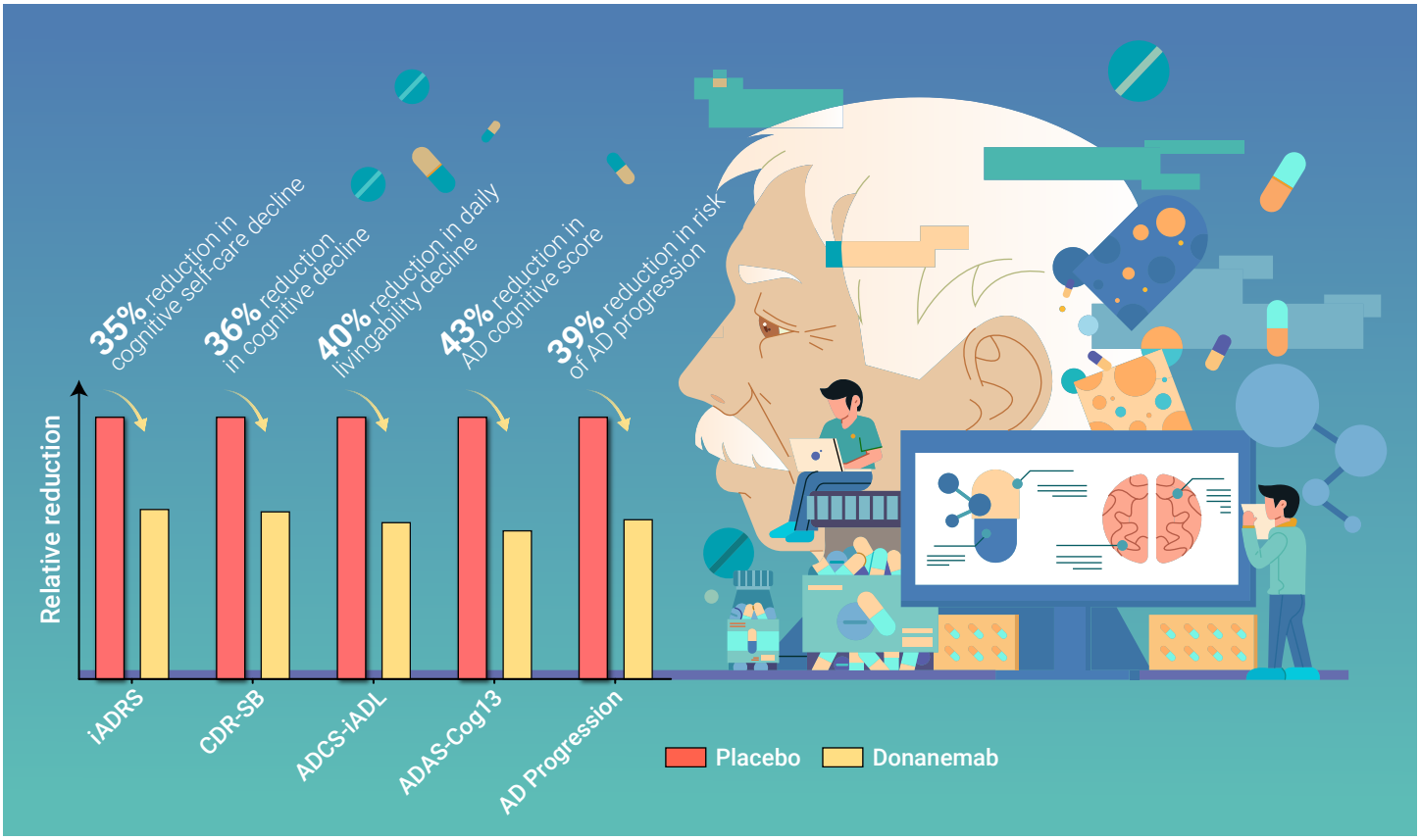

Figure 1. The latest TRAILBLAZER-ALZ 2 clinical trial data of Lilly's Donanemab Donanemab showed a 35% slower decline in the primary endpoint (Integrated Alzheimer's Disease Rating Scale, iADRS) compared to placebo in the trial, while an important key secondary endpoint (Clinical Dementia Rating-Sum of Boxes, CDR-SB) showed a 36% reduction. Donanemab had a 40% reduction in the ability to perform activities of daily living at 18 months (measured by Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory, ADCS-iADL). As well, participants on donanemab had a 40% less decline in ability to perform activities of daily living at 18 months (measured by Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory, ADCS-iADL). More importantly, patients receiving Donanemab showed a 43% reduction in Alzheimer's Disease Assessment Scale-Cognitive (the 13-item Alzheimer's Disease Assessment Scale – Cognitive) score compared to placebo, and for these participants, the risk of progressing to the next stage of Alzheimer's disease (AD) was reduced by 39%.

and many people believe that the data from two pivotal phase III clinical trials of Aducanumab are insufficient to demonstrate its effectiveness in the treatment of AD. Lecanemab, a humanized IgG1 monoclonal antibody, has a high affinity for soluble amyloid-β (Aβ) protofibrils and is more toxic to neurons than monomers or insoluble fibrils, which has been shown to similarly reduced the levels of amyloid markers in the brains of patients with early AD. In a phase III clinical trial, Lecanemab caused a lower decline in cognitive and functional measures than the placebo at 18 months of use but was associated with adverse events. Longer clinical trials are therefore still needed to determine the efficacy and safety of Lecanemab in early AD.

Let's look at Donanemab of Eli Lilly, in a previous 18-month phase 2 trial (TRAILBLAZER-ALZ trial, a multicenter, randomized, double-blind, placebo-controlled phase 2 study, NCT03367403), the researchers found that Donanemab showed robust amyloid plaque reduction in early symptomatic AD patients measured on positron emission tomography (PET) and was superior to placebo in the primary outcome, showing a 32% reduction in disease progression from baseline to 76 weeks on Integrated Alzheimer's Disease Rating Scale (iADRS), patients with early symptomatic AD receiving Donanemab experience slower rates of cognitive decline than placebo recipients, demonstrating that Donanemab effectively reduced amyloid plaques and slowed pathological progression in AD, although this improvement did not halve disease progression, this phenomenon is undoubtedly an optimistic signal for Donanemab performance in longer-term clinical trials.[1] Donanemab has recently aroused widespread concern because of its eye-catching effectiveness data in phase III clinical trials. More excitingly, Lilly published data from a clinical trial directly competing with Aduhelm in December last year.[2] In this phase III clinical trial of TRAILBLAZER-ALZ 4 study, 37.9% of subjects treated with Donanemab achieved brain amyloid clearance (achieved brain amyloid plaque levels of < 24.1 Centiloids) at 6 months, compared with 1.6% of subjects treated with Aduhelm. In the intermediate tau subpopulation, 38.5% of Donanemab-treated participants achieved clearance of brain amyloid at 6 months, compared with 3.8% of Aduhelm-treated participants, which was only 10-fold lower than Donanemab-treated participants. Finally, in a key secondary outcome, Donanemab reduced brain amyloid levels in patients with early AD by 65.2% (compared to baseline) at 6 months, much greater than 17.0% for Aduhelm.[3] These significant amyloid plate clearance effects have laid a solid foundation for Donanemab to improve AD progression, but the indicator of "reducing iADRS score" has been slightly flawed in clinical trials, so this TRAILBLAZER-ALZ 2 trial has become Donanemab's rightful battle.[4] Previously, Lecanemab manufactured by Biogen and Eisai has been shown to translate the ability to "de-plaque" into the ability to clinically "delay AD progression", Donanemab with the same Mechanisms of Action (MOA) is bound to be compared to it. The primary endpoint of this trial was the change of iADRS score in patients with early AD after 76 weeks of treatment, and Donanemab 's trial was more comprehensive than Lecanemab in terms of secondary endpoints and considered the safety dimension more comprehensively. The analysis population for this study consisted mainly of patients with an intermediate level of tau and clinical symptoms of AD (n = 1182) and some patients with high tau levels (n = 552). According to Lilly's published results, some of the data for these participants in this trial are shown in Figure 1.[4] In the first two populations, Donanemab was able to slow the progression of cognitive decline by 35% at 18 months as judged by changes in the primary endpoint (iADRS) ($p < 0.0001$), while an important key secondary endpoint (Clinical Dementia Rating-Sum of Boxes, or CDR-SB) showed a 36% reduction in the rate of cognitive decline in subjects receiving Donanemab over 18 months ($p<0.0001$), which was 9% higher than that of Lecanemab. In an additional primary analysis of all participants, the study also grouped patients with high tau and intermediate tau representing later stages of disease progression (n = 1736) and found that Donanemab also showed significant positive results in all clinical endpoints ($p < 0.001$), with CDR-SB and iADRS showing 29% and 22% slowing of cognitive decline, respectively. Although this effect is reduced compared to the overall population, it remains stronger than Lecanemab. Of all patients in this trial, 52% of participants treated with Donanemab completed the course within 1 year, 72% completed the course by 18 months as a result of achieving plaque clearance, and participants taking Donanemab had a 40% less reduction in the ability to perform activities of daily living at 18 months (measured by Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory, ADCS-iADL). More importantly, Donanemab showed a significant effect in controlling AD progression, with a 39% reduction in the risk of progression to the next stage of disease in participants taking Donanemab compared with placebo (CDR-Global Score, $p<0.001$). The incidence of amyloid-related imaging abnormalities (ARIA) following the use of Donanemab was consistent with the TRAILBLAZER-ALZ Phase 2 study on relevant results from safety assessments.[5] In the Donanemab-treated group, ARIA-E developed in 24.0% of all subjects, with associated symptoms caused by ARIA-E in 6.1% and ARIA-H in 31.4% of subjects, compared with 13.6% in the placebo group. Even though most ARIA cases were mild to moderate, there were 3 deaths, comparable to Lecanemab.

Overall, Donanemab has achieved satisfactory results in the treatment of early AD. As a monoclonal antibody drug with the same MOA, Donanemab has been arguably stronger than Aducanumab in all aspects, and Donanemab can also show slight advantages in competition with Lecanemab, including in the medication cycle (Lecanemab requires biweekly injections and Donanemab only monthly injections). Of course, the subjects and effectiveness evaluation indicators of phase III clinical trials of the two drugs are slightly different, so the battle between Donanemab and Lecanemab needs to wait for the final patient medication effect to be evaluated. From the results of this clinical trial, Donanemab also faces some problems, and we can find that the effectiveness of 35% of cognitive impairment relief is mainly achieved in patients with moderate tau levels, and this effectiveness value decreases to 22% when the range of subjects expands, that is, patients with high tau levels are included. In addition, medication safety may also become a problem faced by the use of Donanemab. The incidence of ARIA-E and ARIA-H mentioned above in the Donanemab treatment group was higher than that of Lecanemab (the incidence of ARIA-E was 24% in Donanemab, 6.1% in ARIA-E with symptoms and 31.4% in ARIA-H, while these three indicators were 12.6%, 2.8% and 17.3% in Lecanemab clinical trials), which is another problem that Lilly urgently needs to solve at present. Donanemab has a long way to go to become the first drug to open up the vast market for AD treatment.

REFERENCES

1. Mintun, M.A., Lo, A.C., Duggan Evans, C., et al. (2021). Donanemab in Early Alzheimer's Disease. N Engl J Med ***384***, 1691–1704.
2. Shcherbinin, S., Evans, C.D., Lu, M., et al. (2022). Association of Amyloid Reduction After Donanemab Treatment With Tau Pathology and Clinical Outcomes: The TRAILBLAZER-ALZ Randomized Clinical Trial. JAMA Neurol ***79***, 1015–1024.
3. Lilly Shares Positive Donanemab Data in First Active Comparator Study in Early Symptomatic Alzheimer's Disease. Lilly, https://investor.lilly.com/news-releases/news-release-details/lilly-shares-positive-donanemab-data-first-active-comparator.
4. Lilly's Donanemab Significantly Slowed Cognitive and Functional Decline in Phase 3 Study of Early Alzheimer's Disease. Lilly, https://investor.lilly.com/news-releases/news-release-details/lillys-donanemab-significantly-slowed-cognitive-and-functional.
5. Gueorguieva, I., Willis, B.A., Chua, L., et al. (2023). Donanemab Population Pharmacokinetics, Amyloid Plaque Reduction, and Safety in Participants with Alzheimer's Disease. Clin Pharmacol Ther, 10.1002/cpt.2875.

DECLARATION OF INTERESTS

The authors declare no competing interests.