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Review Article

Prospective role of Donanemab and amyloid beta therapies in early Alzheimer's disease: A systematic review

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ABSTRACT

Amyloid-β (Aβ) peptide accumulation in the brain, leading to amyloid plaques, is considered to be the starting point of Alzheimer's disease. It is believed that these plaques impair cognitive and functional capacities and induce neurodegeneration. Research on uncommon genetic variants that either increase or decrease the quantity of Aβ deposited offers proof that amyloid plaques are involved in the disease's progression. Early-stage amyloid plaque buildup increases the likelihood that moderate cognitive impairment may progress to dementia.Donanemab, a humanized IgG1 antibody, targets an N-terminal pyroglutamate Aβ epitope that is unique to plaques that have already begun to develop. It is specific to this epitope and has no known clinical effect. Furthermore, it doesn't show any off-target binding to neurotransmitters, their receptors, or other Aβ species. In this systematic review, we first collect the necessary information after carefully reviewing four different study articles. After the data is collected, we evaluate it and create a graph to compare those study articles.

1. Introduction

Alzheimer's disease, the main cause of dementia, has been designated as a global public health priority.There will probably be 152.8 million Alzheimer's disease cases worldwide by 2050. Many clinical trials aimed at finding efficacious AD disease-modifying therapies have been unsuccessful over the last 20 years. Eliminating the extracellular amyloid-β (Aβ) plaques in the brain is one of the approaches being researched for the treatment of AD. From a molecular perspective, AD is distinguished by two pathological hallmarks in the central nervous system (CNS): the formation of extracellular amyloid plaques from amyloid-β peptides and neurofibrillary tangles formed of aggregated and hyperphosphorylated tau. Reducing the amount of amyloid plaques is the goal of many clinical trials utilizing therapeutic chemicals; these trials have shown a strong correlation between the rates of amyloid-related imaging abnormalities (ARIA), the amount of plaques removed, and the efficacy of treatment.[1]

Alzheimer's disease pathogenesis is a proteinopathy caused by misfolded and aggregating proteins. This pathway is shared by several other neurodegenerative diseases, including spongiform encephalopathies, light chain amyloidosis, Parkinson's disease, and Huntington's disease. One common characteristic of numerous illnesses is the conversion of normally soluble proteins into insoluble fibrillar clumps. Each proteinopathy is characterized by a different fibrillar aggregation, such as tau neurofibrillary tangles and amyloid-β (Aβ) plaques in AD, Lewy bodies of α-α-synuclein in PD, or amyloid deposits of an immunoglobulin light chain in AL.[2]

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With aging, the amyloid accumulation that the protein homeostasis system typically prevents reduces. The damaging Aβ oligomer hypothesis, which is validated by in vitro, in vivo, and ex vivo models, suggests that the primary agents in AD pathogenesis are the Aβ oligomers rather than amyloid plaques. Elevated amounts of oligomers have been associated with AD because they are the most toxic and pathogenic form of Aβ and are found in AD brains. Thus, experimental data provides support for a pathogenic mechanism in which Alzheimer's disease neuropathology and cognitive decline are caused by Aβ oligomers' toxicity to neurons. Lowest possible molecular weight Aβ oligomers, which are the most aqueously diffusible, have the capacity to compromise neuritis integrity and synaptic plasticity.

There has been a lot of research recently on the physical basis of oligomer toxicity. It has been discovered that pairs of toxic and non-toxic oligomers are present in alpha-synuclein, Aβ42, and other proteinopathies. The different pairs have been found to have similar physicochemical properties, such as a higher proportion of hydrophobic residues exposed to solvents. These residues have a significant attraction for biological membranes and can induce disruption and cellular malfunction. In summary, hydrophobic residues exposed to solvents appear to be an essential feature shared by all hazardous oligomers.[3]

Additionally, oligomers can contribute to the pathogenesis of AD by spreading from one cell to another or by forming new fibrils after being absorbed by neurons. Aβ oligomers accelerate synaptic breakdown, decrease spine density, and rapidly decrease the membrane expression of memory-related receptors in cultures of hippocampus neurons. The biological mechanisms that ultimately lead to neuronal cell death and neurodegeneration include membrane disruption, intracellular Ca2+ influx mediated by N-Methyl-D-aspartate (NMDA) and Adenosine Monophosphate (AMP) receptors, mitochondrial dysfunction, production of reactive oxygen species (ROS), lipid peroxidation, an elevated caspase-3 response, and aberrant protein-protein interactions. It's crucial to keep in mind that mAbs are meant to target Aβ oligomers in the AD therapy research pathway, as Lecanemab has demonstrated.

Conversely, aminosterols represent a promising family of small molecules since they eliminate the toxicity of the hazardous oligomers Aβ40, Aβ42, and α Syn by preventing them from adhering to cells. Alzheimer's disease (AD) research and therapeutic trials are once again centeredaround the increasingly compelling theory that amyloid-beta (Aβ) peptides and amyloid buildup in the brain cause AD. The FDA's recent approval of aducanumab and lecanemab, two anti-Aβ monoclonal antibodies, for the treatment of AD patients, serves as evidence of this. These "transformative treatments that redefine AD therapeutics," however, do not, according to scientific evidence, slow the course of AD and minimize cognitive decline.[4]

They do reduce the amount of amyloid in the brain, but because they encourage brain hemorrhage and oedema, they can also have a serious negative impact on health. The creation and approval of anti-amyloid disease-modifying treatments for Alzheimer's disease (AD) have advanced significantly in recent years.

The FDA approved Aducanumab in June 2021, making it the first medication of its kind to be approved via the fast approval pathway for mild AD and mild cognitive impairment. Many experts were skeptical of this medication because of methodological problems and the drug's failure to consistently show a correlation between removing amyloid plaques and slowing cognitive decline in its two innovative phase III clinical trials.

Produced in the same patient population with moderate AD and MCI by the same companies, it received traditional FDA clearance in July 2023. Unlike Aducanumab, Lecanemab will get financial support from the US Centres for Medicare & Medicaid Services to promote availability to eligible patients. That same month, groundbreaking positive data from a phase III clinical trial with a third monoclonal antibody, Donanemab, were reported at the Alzheimer's Association international conference (AAIC).[5]

These discoveries give individuals with this debilitating illness additional hope and treatment alternatives. Positive results from the TRAILBLAZER-ALZ 2 Phase 3 trial were released by Eli Lilly and Company (NYSE: LLY). The experiment showed that Donanemab significantly lowered the rate of cognitive and functional loss in people with early-stage Alzheimer's disease symptoms. The integrated Alzheimer's Disease Rating Scale (iADRS) change from baseline to 18 months was accomplished by Donanemab.

The primary goal of the iADRS is to evaluate cognitive capacities and daily activities such as driving, managing finances, engaging in hobbies, and conducting news-related conversations. All of the secondary goals related to cognitive and functional decline were met, and the treatment benefits were equivalent in size and statistically significant. Given these results, Lilly intends to speed global regulatory applications, with the goal of submitting this quarter to the Food and Drug Administration (FDA) in the United States. Lilly plans to work with the FDA as well as other foreign regulatory agencies to speed the traditional approval procedure.[5]

2. Findings from Literature Review of RCTs

Before starting to write this review, we read the article where this work was published very attentively. We published this comparison review article based on four research publications after evaluating the work based on clinical trials. Therefore, we start by going over the research article that was published in "The New England Journal of

Medicine" on May 6, 2021, under the title "Donanemab in Early Alzheimer's Disease." We now know a great lot about donanemeb and how it can be used to treat Alzheimer's after reading this research. They use an original methodology in their study, and the results are quite remarkable. We addressed that in our article.[6]

Of the 1955 patients who were assessed for eligibility, 257 were involved in the study; 126 received a placebo and 131 received Donanemab. Of these, the majority were selected. Their results showed that the placebo group's baseline iADRS score at 76 weeks was −10.06, while the Donanemab group's baseline score was −6.86. They also noted that the anticipated percent change in the iADRS score at 76 weeks between the donanemab group and the placebo group, when analyzed using the MMRM, was similar to the Bayesian disease progression ratio for the entire 18-month period.

Using the Bayesian disease progression ratio, the posterior probability of at least 25% slower disease progression in the Donanemab group relative to the placebo group was computed. Further research findings revealed that, at 76 weeks, there was a −0.36, −1.86, and 1.21 difference in the CDR-SB score, ADAS-Cog13 score, ADCS-iADL score, and MMSE score between the Donanemab group and the placebo group, respectively, compared to baseline.[6]

This paper concludes that the reduction in the iADRS score by 3.20 points in the Donanemab group was less than that of the placebo group, based on the primary analysis of this trial, which included individuals with early symptomatic Alzheimer's disease and Donanemab, an amyloid plaque specific intervention. The iADRS has a range of 0 to 144. The trial was powered to show a 6-point difference; this goal was not met. Our goal was to find a medicine that could delay the progression of Alzheimer's disease by at least half.

On this scale, the minimal clinically significant difference is yet to be determined. Although the MMRM studies did not provide clinical evidence for the effectiveness of donanemab, the drug's efficacy was supported in a Bayesian disease progression model with reasonable intervals that were not multiple-compared. Compared to the placebo group, the amyloid plaque level was lower in the Donanemab group; however, we were unable to show a relationship between this reduction and specific clinical outcomes.[6]

The second study we reviewed was entitled "Donanemab (LY3002813) of a Prospective Phase 1b Study in Alzheimer's Disease: Rapid and Sustained Reduction of Brain Amyloid Measured by Florbetapir F18 Imaging" and was published in the journal "J PrevAlz Dis" in year 202. Out of the 276 patients who were enrolled, 61 patients met the entry criteria and were randomly assigned to the 10-, 20-, and 40-mg/kg single dose cohorts, respectively; 10

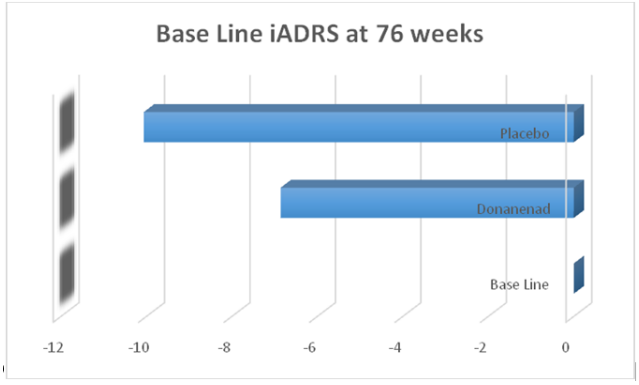

Figure 1: Comparative study between donanemab and placebo at 76 weeks.

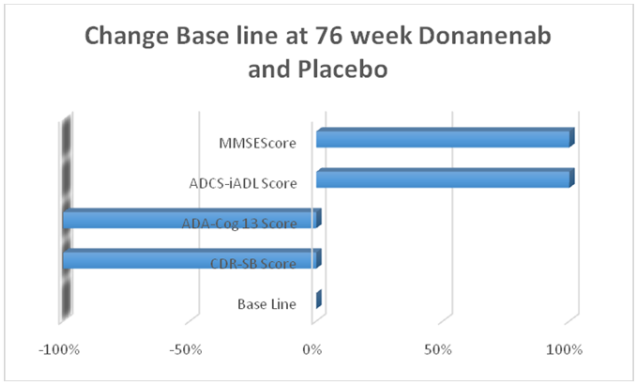

Figure 2: Comparative study between donanemab and placebo at 76 weeks compared to baseline.

patients were assigned to the 10-mg/kg Q2W cohort for a duration of 24 weeks, while 8 and 10 patients were assigned to the 10-mg/kg Q4W and 20-mg/kg Q4W clinical trials, respectively.[7]

Donanemab doses, both single and multiple, systematically reduced the quantity of cerebral amyloid (Centiloid units) assessed by PET from Week 12 to Week 72 when compared to baseline. Based on amyloid PET least squares analysis, the mean centiloid changes at Week 24 for each of the three donanemab doses were as follows: -16.5 for 10-mg/kg IV; -40.0 for 20-mg/kg IV; and -49.6 for 40-mg/kg IV. However, in the placebo group, there was no appreciable drop in Florbetapir.

PET was 90.9 centilitres at 72 weeks, down from 104.4 centilitres at baseline. The equivalent Centiloid alterations for a number of doses at Week 24 were -55.8 10-mg/kg Q2W, -50.2 ; 10-mg/kg Q4W, and -58.4 ; 20-mg/kg Q4W. Patients in the 20 mg/kg Q4W group tended to experience more plaque reduction early in the study compared to patients in either of the two 10 mg/kg multiple dosing cohorts. Following dosage, brain amyloid levels were consistently reduced in all single- and multiple-dose

groups without significantly re accumulating for up to 72 weeks.This work concludes that, after either a single or several doses of Donanemab, there was no appreciable re-accumulation of amyloid plaque at 72 weeks. [7]

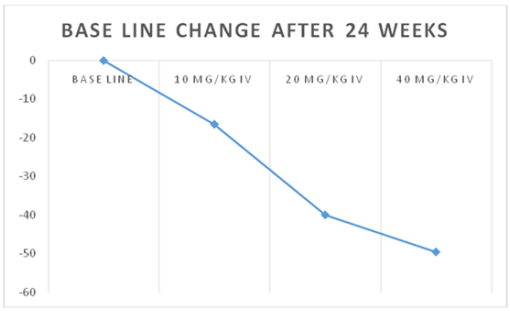

Figure 3: Symptomatic changes after 24 weeks with the experimental drug

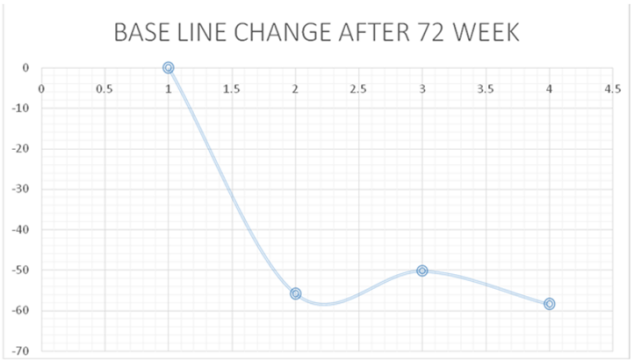

Figure 4: Overall changes after 72 weeks of therapy.

The third paper was published by "Translation Research Clinical Interventions" on February 5, 2021, and was named "Donanemab dose-escalation study in Alzheimer's disease." As to their report, the study involved 63 participants, comprising 30 males and 33 women, with ages ranging from 21 to 89. Their study's conclusions show that, as compared to a placebo, there was a statistically significant decrease in cerebral amyloid as determined by PET after 28 weeks at the maximal dose of 10 mg/kg. [8]

The results showed that cortical amyloid levels were consistently lower in patients who had three to five doses of Donanemab (10 mg/kg). The 10-mg/kg IV arm showed a mean SUVR change from baseline of −0.26 and a mean centiloid change from baseline of −44.4, compared with the little change from baseline in the pooled placebo arms. These results show that brain amyloid has decreased by 40% to 50% on average.

The conclusion drawn in this article is that Donanemab up to 10 mg/kg was well tolerated overall. Donanemab single dose injection at dosages ranging from 0.1 to 3.0 mg/kg resulted in a mean terminal elimination half-life of 4 days at 10 mg/kg. In individuals with AD, donanemab 10 mg/kg intravenous scan lowers amyloid buildup, despite its shorter half-life than expected. [8]

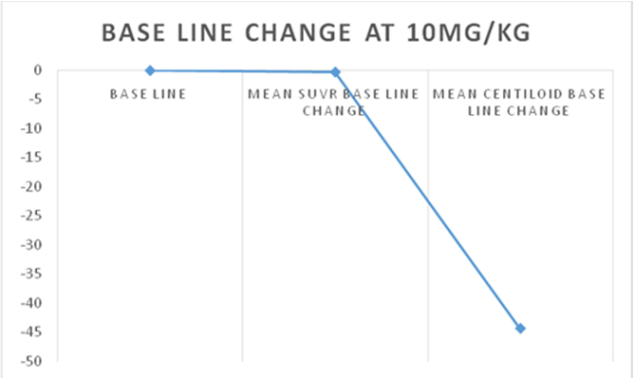

Figure 5: Some facets of study of the drug in clinical settings at 10 mg/kg.

In the fourth publication, "Donanemab Population Pharmacokinetics, Amyloid Plaque Reduction, and Safety in Participants with Alzheimer's Disease," which was published on "Clinical pharmacology & Therapeutics" in June 2023, we noticed that they compare research work with the "TRAILBLAZER-ALZ" trial.

Accordingly, the fourth paper discusses that 304 subjects from the TRAILBLAZER-ALZ trial and phase 1b studies were randomized to either a placebo or donanemab. The results of TRAILBLAZER-ALZ show a steady drop in amyloid plaque levels even when divided by the length of the final donanemab dosage, which terminated at 24 or 52 weeks. [9]

The final exposure response model was used to replicate the decrease in amyloid plaque after participants were divided into groups according to when they had taken their last dose of donanemab and placebo. The 5th, 95th, and median percentiles of the actual observations were compared with the models' 95% confidence interval (CI) and median. A VPC for the removal of amyloid plaque was also carried out to confirm the accuracy of the model. Plaque elimination half-life of 10.2 years and treatment effect-linked threshold concentration of 4.43 μg/ml were features of the final exposure response model. Within the investigated dose range, increased exposure had no further effect on the amount of amyloid removed. [10]

The influence of baseline amyloid plaque level on the time it takes to reach amyloid levels of < 24.1 Centiloids and < 11 Centiloids was investigated by simulating the change in amyloid plaque level, given the dosing regimen and stopping criteria in TRAILBLAZER-ALZ. All told, two thousand people were simulated. The baseline amyloid levels' quartiles were determined. The proportion of participants exhibiting amyloid plaque concentrations below 24.1

A simulation was carried out for every baseline quartile, spanning from centiloids to fewer than 11 centiloids throughout time, using observed data from the two investigations. More participants attained amyloid plaque levels < 24.1 centiloid and < 11 centiloid in less time when their baseline levels of amyloid plaque were lower. To investigate the impact of ADA titer, two extreme scenarios were simulated in which participants were expected to maintain an ADA titer for the duration of the study.

Thus, the simulations should represent a "worst-case" scenario for how ADA impacts amyloid plaque clearance. The simulations show that there is very little effect of ADA titer on plaque clearance, even at the highest titer (1:327,680). The percentage of participants expected to achieve amyloid plaque levels < 24.1 centiliters and < 11 centiliters throughout time were similar whether there was no ADA titer and a maximal ADA titer of 327,680.

"47% of participants on donanemab showed no decline on CDR-SB, a key measure of disease severity at 1 year" stated "TRAILBLAZER-ALZ," produced by "Eli Lilly and Company." 52% of patients completed their course of treatment in less than a year after their plaque was eliminated, and 72% completed it in less than 18 months. At 18 months, participants on donanemab saw a 40% loss in their capacity to execute activities of daily living ($p<0.0001$), according to the instrumental Activities of Daily Living Inventory (ADCS-iADL) of the Alzheimer's Disease Cooperative Study.[10]

Donanemab users had a 39% lower probability of progressing to the subsequent stage of the illness in comparison to placebo users (CDR-Global Score, HR=0.61; $p<0.001$). Donanemab is an investigational drug that targets amyloid plaque; Eli Lilly and "Company" evaluated its safety and efficacy in a randomized, double-blind, placebo-controlled study. The study required participants to have a diagnosis of early-stage symptomatic AD, which includes proven AD neuropathology and moderate cognitive impairment or mild dementia.

After individuals reached a predefined level of amyloid plaque removal, donanemab therapy was discontinued. Tau is a brain protein that has been utilized as a predictive biomarker for Alzheimer's disease progression and was used to stratify participants in TRAILBLAZER-ALZ 2. "The primary analysis sample (n=1182), which included people with intermediate tau levels and clinical signs of Alzheimer's disease, constituted the study's power. In this group, the Clinical Dementia Rating-Sum of Boxes, or CDR-SB, important secondary endpoint showed a 36% slowing of decline ($p<0.0001$) over an 18-month period, while the iADRS primary aim showed a 35% slowing of deterioration ($p<0.0001$)."[10]

3. Discussions

According to these studies, donanemab is a humanized IgG1 antibody that primarily targets the pyroglutamate Aβ epitope located at the N-terminus, which is only seen in plaque that has formed. It has no known clinical impact and is unique to this epitope. Moreover, it exhibits no off-target binding to other Aβ molecules, neurotransmitters, or their receptors.

The primary analysis of this study was conducted on individuals with early symptomatic Alzheimer's disease using Donanemab, an amyloid plaque-specific treatment. The score reduction for the Donanemab group was 3.20 points less than that of the placebo group, according to the data. The range of the iADRS is 0 to 144. The trial's power was intended to demonstrate a 6-point difference (basis point drops for placebo and Donanemab of roughly 12 and 6 points, respectively); however, this target was not achieved. Our mission was to discover a medication that may at least partially halt the advancement of Alzheimer's disease. The lowest clinically meaningful difference on this scale has not yet been identified. Most investigations have demonstrated that Donanemab decreases amyloid build-up and plaque in the brains of AD patients.[11]

4. Source of Funding

None.

5. Conflict of Interest

None.

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