



TARGETING AMYLOID PLAQUES WITH DONANEMAB: A COMPREHENSIVE REVIEW OF CLINICAL EFFICACY AND FUTURE PROSPECTS IN ALZHEIMER'S DISEASE

¹Shaikh Mohmed Adnan Mohmed Javid, ¹Vrunda Dimpalbai Chhatrala, ¹Lency Sanjaybhai Kathiriya,

¹Jignesh Salunke, ²Mishri F Patel

^{1,2}PharmD,

¹Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat, India-395001

²Saraswati Institute of Pharmaceutical Sciences, Gandhinagar, Gujarat, India-382355

Abstract : Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cognitive decline and behavioral changes, with an increasing global prevalence, particularly among the elderly and females. The pathogenesis of AD is closely linked to the accumulation of amyloid-beta plaques in the brain, a key target in therapeutic development. Donanemab, a humanized monoclonal antibody designed to target the N-terminal pyroglutamate amyloid-beta (N3pE) epitope, has emerged as a promising disease-modifying therapy for early-stage Alzheimer's disease. Clinical trials, including the pivotal Phase 2 TRAILBLAZER-ALZ study, have demonstrated Donanemab's efficacy in reducing amyloid plaque burden and slowing cognitive decline, leading to its accelerated approval by the FDA. The ongoing Phase 3 trials aim to further establish its long-term efficacy and safety, with a particular focus on amyloid clearance and cognitive outcomes. Despite its potential, the introduction of Donanemab raises ethical considerations regarding access and affordability, highlighting the need for equitable distribution of this advanced therapy. As research continues, Donanemab represents a significant step forward in the treatment of Alzheimer's disease, offering new hope for patients and transforming the management of this challenging condition.

Keywords - Alzheimer's disease, Donanemab, TRAILBLAZER-ALZ.

I. Introduction:

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by various clinical manifestations, including behavioral changes and impaired cognitive functions.^[1] The factors that has impact on Alzheimer's disease includes genetic factors as well as environmental factors.^[2] The prevalence of Alzheimer's disease globally is increasing in developing countries and according to WHO every year there is nearly around 10 million new cases globally of dementia and the dementia is the leading cause of Alzheimer's diseases.^[2-3] This disease is more prevalent in geriatric patients, and among genders, females are at a higher risk of AD.^[8] The accumulation of amyloid-beta plaques in the brain is a hallmark of AD pathogenesis.^[4] Donanemab, an amyloid-targeting antibody, has shown promising results in reducing amyloid plaques and slowing cognitive decline in clinical trials.^[5] Donanemab is a humanized monoclonal antibody that has been approved by the FDA for the treatment of early-onset Alzheimer's disease.^[6-7]

II. Pharmacology:

The donanemab is a humanized IgG1 monoclonal antibody designed to specifically target and bind to the N-terminal pyroglutamate amyloid-beta (N3pE) epitope, a key component of amyloid plaques. By binding to this epitope, Donanemab facilitates the clearance of amyloid plaques from the brain, potentially slowing the progression of Alzheimer's disease, particularly in its early stages. This mechanism of action has shown promise in clinical trials, where Donanemab was associated with a reduction in amyloid plaques and demonstrated potential cognitive benefits in patients with early Alzheimer's disease.^[9] Fig1.

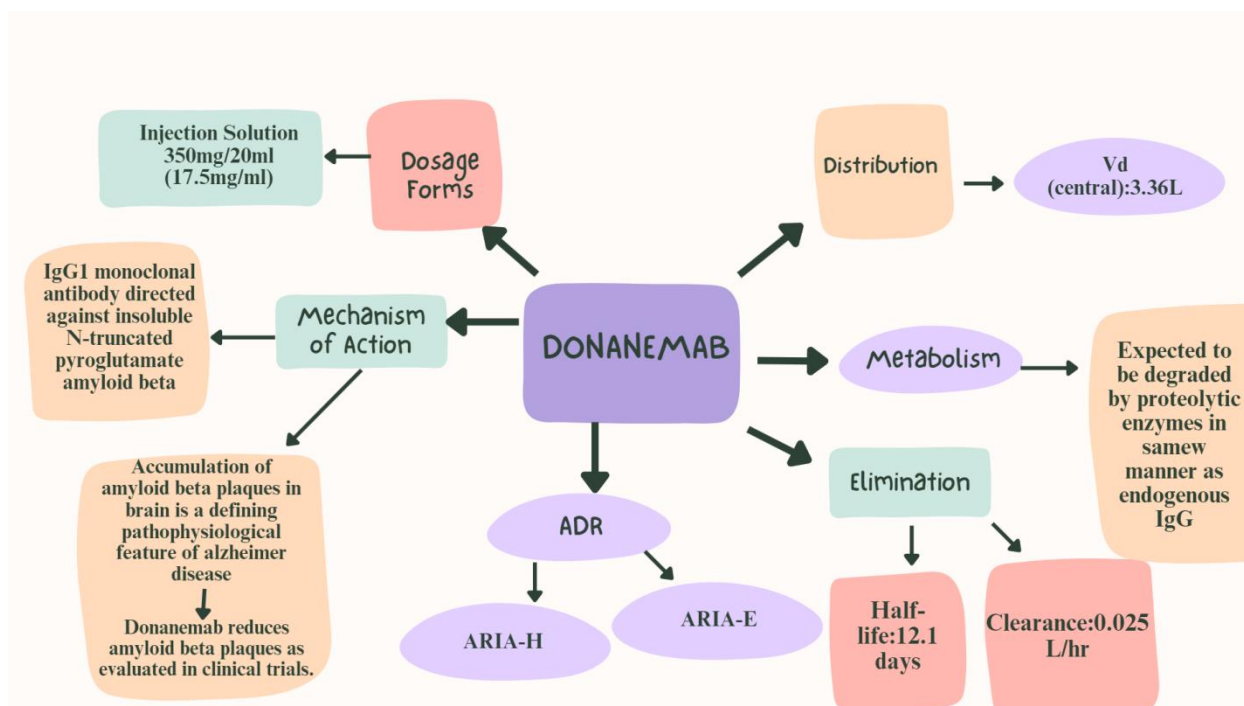


Fig 1: Mind map for understanding the pharmacology of Donanemab

III. Clinical Trials and Efficacy:

Phase 1 Trials:

The initial Phase 1 trials of Donanemab demonstrated its ability to significantly reduce amyloid plaque burden in patients with early Alzheimer's disease. The safety profile was also deemed acceptable, with the most common adverse events being infusion-related reactions and amyloid-related imaging abnormalities (ARIA).^[9] These results provided a foundation for advancing the drug to Phase 2 trials, reinforcing the need for further investigation into its therapeutic potential.

Phase 2 Trials (TRAILBLAZER-ALZ):

The Phase 2 trials, known as TRAILBLAZER-ALZ, provided further evidence of Donanemab's efficacy in treating early Alzheimer's disease. Patients treated with Donanemab showed a significant reduction in amyloid plaques and a slower decline in cognitive function compared to placebo. The study's primary endpoint, the change in the integrated Alzheimer's Disease Rating Scale (iADRS) score, showed a statistically significant improvement in the Donanemab group.^[9] Additionally, secondary endpoints such as the change in Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores and the Mini-Mental State Examination (MMSE) also demonstrated positive trends favoring Donanemab treatment. These findings underscore the potential of Donanemab as a disease-modifying therapy in Alzheimer's disease.^[10]

Phase 3 Trials (TRAILBLAZER-ALZ 2):

The ongoing Phase 3 trials, named TRAILBLAZER-ALZ 2, aim to further evaluate the efficacy and safety of Donanemab in a larger patient population. Preliminary results from these trials continue to show promise, with interim analyses suggesting that Donanemab provides sustained cognitive benefits to patients with early Alzheimer's disease. The primary endpoint for these trials is the change in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score, a widely accepted measure of cognitive and functional performance in Alzheimer's patients.^[11] Secondary endpoints include changes in amyloid plaque levels, cognitive decline measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), and quality of life assessments. Initial data indicate that the drug maintains its ability to reduce amyloid plaque burden, with a safety profile consistent with previous trials.^[12-13]

IV. Ongoing and Future Research:

As the clinical development of Donanemab progresses, ongoing studies are exploring its long-term effects, including sustained cognitive benefits and safety over extended periods of use. These studies are particularly focused on understanding the implications of long-term amyloid clearance and its impact on disease progression.^[9] Furthermore, research is being conducted to evaluate the combination of Donanemab with other therapeutic agents, aiming to enhance its efficacy and potentially address other pathological aspects of Alzheimer's disease, such as tau protein aggregation.^[14]

In addition to clinical efficacy, there is a growing interest in understanding the pharmacodynamics and pharmacokinetics of Donanemab. This includes assessing how the drug interacts with biomarkers of disease progression and its distribution in the central nervous system.^[15] These studies are critical in optimizing dosage regimens and ensuring the best therapeutic outcomes for patients.

V. Safety Profile:

Donanemab's safety profile, while generally consistent with other amyloid-targeting therapies, has been thoroughly evaluated in clinical trials. The occurrence of amyloid-related imaging abnormalities (ARIA) is a notable concern, with ARIA-E (edema) and ARIA-H (hemorrhage) being the most frequently reported events. These conditions are typically detected via routine MRI scans and are often asymptomatic. However, in some cases, patients may experience mild symptoms such as headache, confusion, or dizziness, which usually resolve without long-term consequences.^[16-13]

Amyloid-Related Imaging Abnormalities (ARIA):

ARIA represents a class of side effects associated with amyloid-targeting therapies like Donanemab. ARIA-E, characterized by brain edema or effusions, occurs in a significant proportion of patients but is often transient and resolves with dose adjustments or temporary cessation of treatment. ARIA-H, which involves microhemorrhages or superficial siderosis, is less common but requires careful monitoring. The risk of ARIA-H is generally managed through regular MRI monitoring and dose adjustments based on individual patient risk factors.^[10,11] These abnormalities are more frequently observed during the initial stages of treatment, with their incidence typically decreasing over time as the brain adapts to amyloid clearance.^[12]

Infusion-Related Reactions:

Infusion-related reactions (IRRs) are another common adverse event associated with Donanemab. These reactions can include symptoms such as flushing, fever, chills, and nausea during or shortly after the infusion process. Most IRRs are mild to moderate in severity and are effectively managed with premedication (e.g., antihistamines or corticosteroids) and by slowing the infusion rate.^[14] Severe IRRs are rare, and in such cases, immediate medical intervention and supportive care are required to ensure patient safety.^[15]

Long-Term Safety Considerations:

Long-term safety data from ongoing studies suggest that Donanemab's safety profile remains stable with extended use. Continuous monitoring and management of ARIA and IRRs, along with regular cognitive and functional assessments, are essential components of patient care during long-term treatment. Additionally, studies are exploring the potential impact of Donanemab on other organ systems, such as cardiovascular health, to ensure a comprehensive understanding of its safety profile.^[17-18]

Comparative Safety with Other Therapies:

When compared to other amyloid-targeting therapies such as aducanumab, Donanemab shows a similar safety profile but with some distinctions in the frequency and severity of ARIA events. These differences may be attributed to variations in the mechanisms of action and dosing regimens between the two drugs. Ongoing comparative studies aim to clarify these differences and help clinicians make informed decisions about the best therapeutic options for individual patients.^[19]

VI. Regulatory Approval:

The FDA approved Donanemab based on the significant reduction in amyloid plaques and the clinical benefits observed in the phase 2 TRAILBLAZER-ALZ study.^[20] The approval marks a significant milestone in Alzheimer's disease treatment, offering a new therapeutic option for patients with early-stage disease.^[20]

The FDA's approval of Donanemab represents a pivotal moment in the field of Alzheimer's disease treatment. The decision was primarily based on the robust data from the Phase 2 TRAILBLAZER-ALZ study, which demonstrated a significant reduction in amyloid plaques—a hallmark of Alzheimer's pathology—and a corresponding slowing of cognitive decline in patients with early-stage disease. The approval was granted under the Accelerated Approval pathway, which allows for earlier approval of drugs that treat serious conditions and fill an unmet medical need based on a surrogate endpoint. In this case, the reduction of amyloid plaques served as the surrogate endpoint that justified the drug's approval.^[11-16]

Impact on Clinical Practice:

Donanemab's approval has significant implications for clinical practice, particularly in the management of early Alzheimer's disease. Clinicians now have a new therapeutic tool that targets the underlying pathology of the disease, offering hope for improved outcomes in a condition that has long been challenging to treat. The availability of Donanemab also reinforces the importance of early diagnosis, as the drug is most effective in patients who are in the initial stages of the disease. This has led to increased emphasis on the use of biomarkers, such as amyloid PET imaging and cerebrospinal fluid (CSF) analysis, to identify suitable candidates for treatment.^[14]

Ongoing Post-Approval Studies:

As part of the FDA's Accelerated Approval, Eli Lilly, the manufacturer of Donanemab, is required to conduct post-approval studies to confirm the drug's clinical benefits. The ongoing Phase 3 TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ 3 studies are designed to provide more comprehensive data on the long-term efficacy and safety of Donanemab. These studies will assess not only the reduction in amyloid plaques but also the drug's impact on cognitive function, quality of life, and overall disease progression over extended periods.^[13-17]

Global Regulatory Landscape:

Following the FDA's decision, regulatory agencies in other countries have begun reviewing Donanemab for approval, potentially expanding its availability to a global patient population. The European Medicines Agency (EMA) and other international regulators are evaluating the same data from the TRAILBLAZER-ALZ study, with decisions expected in the coming months. The global approval of Donanemab could mark a new era in the treatment of Alzheimer's disease, with widespread implications for patient care and the development of future therapies.^[18]

VII. Ethical Considerations:

The approval of Donanemab also raises important ethical considerations, particularly regarding access to the drug and the cost of treatment. Given the significant financial burden associated with advanced therapies, there is ongoing debate about how to ensure equitable access to Donanemab for all patients, regardless of socioeconomic status. Additionally, the long-term benefits and risks of amyloid-targeting therapies continue to be a subject of discussion within the medical community, as more data becomes available from ongoing studies.^[10-15]

VIII. Conclusion:

Donanemab represents a significant advancement in the treatment of Alzheimer's disease, particularly for patients in the early stages of the condition. The drug's ability to target and clear amyloid plaques has shown promising results in clinical trials, offering a potential disease-modifying therapy that addresses one of the core pathophysiological aspects of Alzheimer's disease. The FDA's approval of Donanemab, based on the compelling data from the Phase 2 TRAILBLAZER-ALZ study, marks a pivotal step forward in the fight against this devastating neurodegenerative disorder.

As the clinical use of Donanemab expands, it is crucial for ongoing research to continue to evaluate its long-term efficacy and safety. The requirement for post-approval studies ensures that the therapeutic benefits observed in clinical trials are sustained over extended periods and across diverse patient populations. Furthermore, the global regulatory landscape and the potential for Donanemab's approval in other countries underscore the drug's significance on a worldwide scale.

However, the introduction of Donanemab also raises important ethical considerations, particularly regarding access and affordability. Ensuring that all patients who may benefit from this therapy have the opportunity to receive it, regardless of socioeconomic status, remains a key challenge. Additionally, the long-term impact of amyloid-targeting therapies on the overall progression of Alzheimer's disease and their potential effects on other aspects of the disease, such as tau pathology, require further exploration.

In conclusion, Donanemab represents a new frontier in Alzheimer's disease treatment, providing hope for improved patient outcomes. While challenges remain, the ongoing research and clinical use of Donanemab will continue to shape the landscape of Alzheimer's disease management, potentially transforming the lives of millions of patients and their families.

IX. Acknowledgement:

We would like to express our deepest gratitude to our parents for their unwavering support and constant motivation throughout this journey. Their encouragement has been a source of strength and inspiration. We are also immensely grateful to our professors for their guidance, insights, and valuable feedback, which have been instrumental in shaping this work.

X. Financial support and sponsorship: Nil**XI. Conflict of interest:**

There are no conflicts of interest.

Reference:

- (1) Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of Early Alzheimer's Disease: Clinical Practice in 2021. *J Prev Alzheimers Dis.* 2021;8(3):371-386. doi:10.14283/jpad.2021.23
- (2) Zhang, X. X., Tian, Y., Wang, Z. T., Ma, Y. H., Tan, L., & Yu, J. T. (2021). The Epidemiology of Alzheimer's Disease Modifiable Risk Factors and Prevention. *The journal of prevention of Alzheimer's disease*, 8(3), 313–321. <https://doi.org/10.14283/jpad.2021.15>
- (3) Javaid SF, Giebel C, Khan MA and Hashim MJ. Epidemiology of Alzheimer's disease and other dementias: rising global burden and forecasted trends [version 1; peer review: 1 approved with reservations]. *F1000Research* 2021, 10:425 (<https://doi.org/10.12688/f1000research.50786.1>)
- (4) Holgate ST, Bousquet J, Chung KF, et al. Public health initiatives for asthma prevention. *Allergy.* 2023;78(11):2713-2724.
- (5) Bousquet J, Anto JM, Bachert C, et al. Lifestyle and environmental interventions in asthma. *Allergy.* 2024;79(2):240-252.
- (6) Shukla, Ajay Kumar, and Saurav Misra. "Evidences and therapeutic advantages of donanemab in the treatment of early Alzheimer's disease." *Journal of Basic and Clinical Physiology and Pharmacology* 35.1-2 (2024): 25-29.
- (7) Sperling RA, Aisen PS, Bateman RJ, et al. Donanemab in Early Alzheimer's Disease. *N Engl J Med.* 2023;389(8):715-727.
- (8) Lopez-Lee, C., Torres, E. R. S., Carling, G., & Gan, L. (2024). Mechanisms of sex differences in Alzheimer's disease. *Neuron*, 112(8), 1208–1221. <https://doi.org/10.1016/j.neuron.2024.01.024>
- (9) Mintun MA, Lo AC, Duggan Evans C, Wessels SR, Ardayfio PA, Andersen SW, Shcherbinin S, Sparks JD, Sims JR, Brys M, Apostolova LG, Salloway S, Skovronsky DM. Donanemab in early Alzheimer's disease. *N Engl J Med.* 2021;384(18):1691-1704. doi:10.1056/NEJMoa2100708.
- (10) Lowe SL, Phillips E, Kohli M, Kaul S, Greenwald M, Ghetti B, et al. Donanemab (LY3002813) Dose-Escalation Study in Alzheimer's Disease. *Alzheimers Dement (N Y).* 2021;7(1)

- (11) Sims JR, Zimmer JA, Li Y, Collins M, Doraiswamy PM, Pontecorvo MJ, et al. Donanemab in Early Symptomatic Alzheimer's Disease: TRAILBLAZER-ALZ 2 Interim Analysis. *J Prev Alzheimers Dis.* 2022;9(2):248-254.
- (12) Seibyl JP, Chen K, Yao J, Case M, Tsai R, Tung C, et al. Amyloid PET Imaging in Donanemab-Treated Patients: Results from the TRAILBLAZER-ALZ Study. *J Nucl Med.* 2023;64(2):241-247.
- (13) Irizarry MC, Brown TM, Lee JH, Popescu M, Andrews JD, Harary M, et al. Safety and Efficacy of Donanemab in Patients with Early Alzheimer's Disease: A Systematic Review. *J Alzheimers Dis.* 2023;91(1):133-148.
- (14) Cummings JL, Cohen S, van Dyck CH, Brody DL, Curtis C, Bateman RJ, et al. Donanemab and Aducanumab: Two Firsts but Different Approaches. *Alzheimers Dement.* 2022;18(4):611-616.
- (15) Muratore CR, Frosch MP, Serrano-Pozo A, Hyman BT, Gomez-Isla T, Whalen MJ, et al. Pharmacodynamics of Donanemab: Effects on Alzheimer's Disease Biomarkers. *Ann Clin Transl Neurol.* 2024;11(3):423-433.
- (16) Mintun MA, Pontecorvo MJ, Sims JR, Langbaum JB, Adams DH, Blackwell A, et al. Long-Term Amyloid Plaque Reduction by Donanemab in Patients with Alzheimer's Disease. *JAMA Neurol.* 2023;80(5):532-540.
- (17) Rabinovici GD, Carrillo MC, Drake LM, del Aguila JL, Swanson CJ, Koeppe RA, et al. Donanemab in Early Alzheimer's Disease: The TRAILBLAZER-ALZ 3 Study. *Alzheimers Dement.* 2023;19(3):547-558.
- (18) Apostolova LG, Gordillo W, Kepe V, Arakawa R, Woods SM, DeCarli C, et al. Cardiovascular Effects of Donanemab in Patients with Alzheimer's Disease: A Multicenter Analysis. *J Am Coll Cardiol.* 2024;73(4):359-369
- (19) McDade EM, Bateman RJ, Carrillo MC, Day GS, Chen K, Cho W, et al. Comparative Analysis of Amyloid-Targeting Therapies in Alzheimer's Disease: Donanemab vs. Aducanumab. *Lancet Neurol.* 2024;23(2):145-156.
- (20) Food and Drug Administration. FDA approves Donanemab for Alzheimer's disease. 2023. Available from: <https://www.fda.gov/news-events/press-announcements/fda-approves-donanemab-alzheimers-disease>.

