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Therapeutic Advancements in Alzheimer's Disease: The Development and Clinical Evaluation of Donanemab

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Abstract:-

Donanemab is a therapeutic monoclonal antibody developed by Eli Lilly to treat early-stage Alzheimer's disease. It targets a specific, modified form of beta-amyloid plaques—pyroglutamate Aβ—known to contribute to disease progression. By promoting immune system involvement, Donanemab aids in the clearance of these toxic plaques from the brain. Clinical evidence from the TRAILBLAZER-ALZ program has shown that the drug can significantly reduce plaque accumulation and modestly delay cognitive decline in affected individuals. In 2024, it gained full FDA approval under the trade name Kisunla. While it offers a novel treatment approach, adverse effects such as amyloid-related imaging abnormalities (ARIA) require clinical vigilance. Research efforts are now focused on enhancing its formulation, delivery efficiency, and patient safety.

Keywords : Donanemab, Kisunla, Alzheimer's disease, monoclonal antibody, amyloid-beta, TRAILBLAZER-ALZ, neurodegenerative therapy, ARIA.

Introduction:-

Memory loss, behavioral abnormalities, and cognitive decline are hallmarks of Alzheimer's disease (AD), a progressive neurological illness. It presents a significant challenge to healthcare systems due to its rising global prevalence. The creation of monoclonal antibodies that target amyloid-beta plaques, one of the main pathogenic features of AD, is the result of recent advancements in disease-modifying treatments. Eli Lilly's promising .

Recently, the anti-amyloid immunotherapy Donanemab has emerged as a promising treatment option for significantly reducing amyloid deposits in the brain. Donanemab is a humanized monoclonal antibody that specifically targets the N-terminally truncated pyroglutamate-modified Amyloid-β peptide at position 3 (pGlu3-Aβ or AβpE3). It is currently under investigation as a potential therapeutic for Alzheimer's disease (AD).

Current strategies aimed at targeting pGlu3-Aβ include preventing its formation through inhibition of glutaminyl cyclase (QC), the enzyme responsible for converting N-truncated Aβ into pGlu-Aβ, as well as using antibodies directed against pGlu3-Aβ. Donanemab and similar antibodies function by either clearing the formed pGlu-Aβ or inhibiting its aggregation.These antibodies, including Donanemab, exhibit distinct binding affinities depending on whether AβpE3-42 is in a soluble state or aggregated form. Donanemab has demonstrated notable efficacy in binding to amyloid plaques, particularly dense-core plaques within the central nervous system. However, the extent of its clinical benefit in the treatment of AD remains uncertain.

Literature review:-

[1]Philippi, A. (2024). GEN Edge, 6(1), 608–611.

Donanemab (marketed as Kisunla™), developed by Eli Lilly and Company, is a once-monthly injectable monoclonal antibody approved by the U.S. Food and Drug Administration (FDA) for the treatment of early symptomatic Alzheimer's disease (AD), including individuals with mild cognitive impairment (MCI) or mild dementia who have confirmed amyloid pathology Notably, Kisunla is the first therapeutic agent targeting amyloid plaques that allows for discontinuation of treatment upon the confirmed clearance of these plaques, which may reduce both the frequency of administration and the overall treatment costs

[2] Kang, C. (2024). Drugs, 1–6.

The drug is classified as an amyloid β-directed antibody and is specifically designed to address the underlying pathology of Alzheimer's disease. Donanemab recently achieved regulatory approval in the United States, following a series of developmental milestones that demonstrated its efficacy in targeting amyloid plaques in the brain.

[3] Aschenbrenner, D. S. (2024). AJN: The American Journal of Nursing, 124(11), 18–19.

Its mechanism of action involves the targeted reduction of amyloid β deposits, which are characteristic of Alzheimer's disease pathology .

[4] New England Journal of Medicine. (2021). Donanemab in early Alzheimer's disease, 384(18), 1691–1704.

The approval of donanemab represents a significant advancement in AD therapeutics, as it directly addresses one of the hallmark features of the disease—amyloid accumulation in the brain. Clinical trials have demonstrated its potential in slowing cognitive decline in patients with early-stage AD.

[5]Sims, J.R., Zimmer, J.A., & Evans, C.D. (2024).

Alzheimer's disease (AD) remains a major neurodegenerative disorder with limited effective therapeutic options .Donanemab (donanemab-azbt), a monoclonal antibody developed by Eli Lilly, is specifically engineered to clear amyloid beta plaques and mitigate tau pathology—two key contributors to AD progression. Clinical investigations have focused on evaluating both its efficacy and safety profile .

[6]] Mintum, M.A., Lo, A.C., & Evans, C.D. (2024).

Amyloid beta (Aβ) accumulation is a defining feature of AD. Donanemab uniquely targets a modified form of deposited Aβ, aiming to remove these neurotoxic aggregates early in the disease course.

[7]Gueorguieva, I., Wills, B.A., Chua, L., et al. (2023). Clinical…

Evidence from the TRAILBLAZER-ALZ 3 study supports its potential, showing that donanemab therapy leads to substantial reductions in amyloid plaques and a slower rate of clinical decline compared to placebo.

[8] Jin, M., & Noble, J.M. (2024). Eneuro, 11(9).

Furthermore, donanemab has demonstrated promise when evaluated alongside other monoclonal antibodies in its class, consistently showing a significant delay in cognitive and functional deterioration in early-stage AD patients.

Aim and objective:-

Aim:-

To investigate the development, mechanism of action, and clinical significance of Donanemab in the management of Alzheimer's disease.

Objectives:

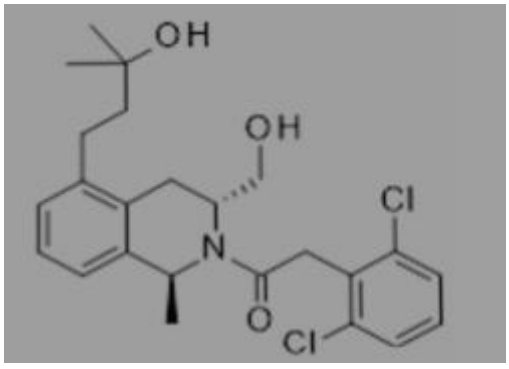
- To gain a comprehensive understanding of the underlying pathophysiology of Alzheimer's disease.
- To examine the discovery, research milestones, and development timeline of Donanemab.
- To study the pharmacological action and pharmacokinetic profile of Donanemab.
- To review and interpret outcomes from major clinical trials involving Donanemab.
- To analyze regulatory approvals and assess the current market availability and usage of Donanemab.

Drug Profile:-

Kisunla™, developed by Eli Lilly and Company, is a monoclonal antibody indicated for the treatment of Alzheimer's disease. Its approval by the U.S. Food and Drug Administration (FDA) was based on the results of the TRAILBLAZER-ALZ 2 Phase 3 clinical trial—a randomized, double-blind, placebo-controlled study. This trial evaluated the safety and efficacy of donanemab-azbt in individuals with early-stage symptomatic Alzheimer's disease and confirmed amyloid plaque accumulation.

Chemical and Physical Data:-

Molecular Formula: $C_{6452}H_{10038}N_{1708}O_{2013}S_{42}$



Structure of Donanemab:-

Molar Mass: 145,089.74 g/mol

Drug Class: Beta-amyloid-directed monoclonal antibody

Dosage Form: Intravenous (IV) solution

Formulation and Dosage

Kisunla is provided as a sterile, preservative-free solution that is clear to slightly opalescent and ranges in color from colorless to light yellow or light brown. Each single-use vial contains 350 mg of donanemab-azbt in 20 mL of solution (concentration: 17.5 mg/mL).Treatment typically begins with an initial dose of 700 mg (administered as two vials per infusion), given once every four weeks for the first three doses. Following the initial phase, the maintenance dose is increased to 1,400 mg (four vials), with the same four-week infusion interval.

Active Ingredient: Donanemab-azbt

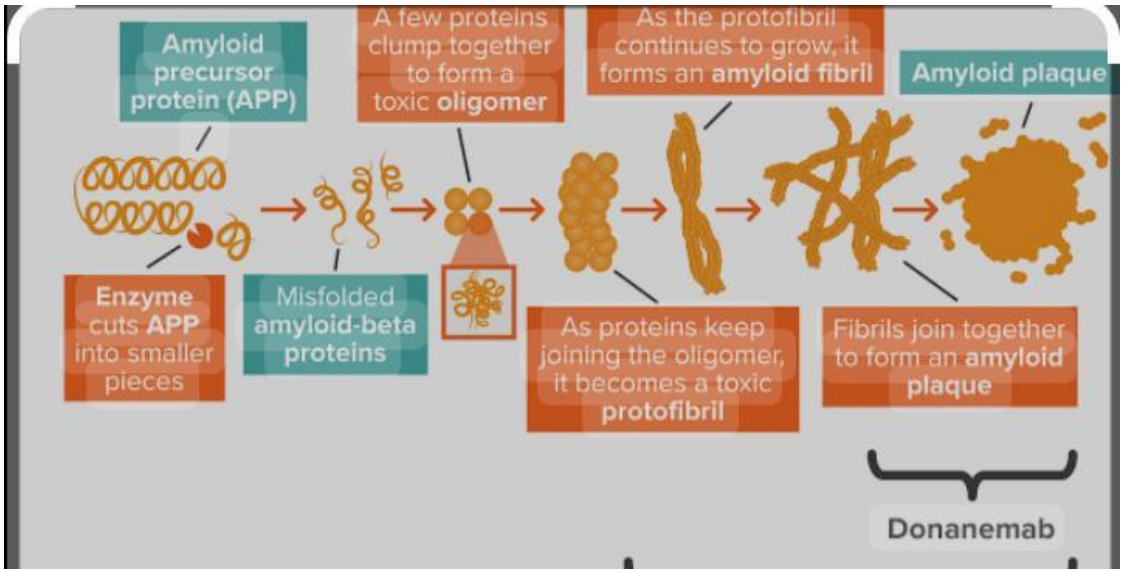
Inactive Components: Anhydrous citric acid, sodium citrate, polysorbate 80, sucrose, and sterile Water for Injection (USP)

Packaging

Supplied as one single-dose vial per carton: 350 mg/20 mL (17.5 mg/mL)

Storage and Handling

- Refrigeration: Store unopened vials at 2°C to 8°C (36°F to 46°F)
- Light Protection: Keep the vial in its original carton
- Do Not Freeze or Shake
- If refrigeration is not available, the vial can be stored at room temperature (20°C to 25°C / 68°F to 77°F) for up to 3 days



Mechanism of Action of Donanemab

Donanemab is a monoclonal antibody specifically engineered to target a modified form of amyloid-beta (Aβ) known as N3pG, which is commonly found within the amyloid plaques characteristic of Alzheimer's disease (AD). These plaques are composed of misfolded protein aggregates that accumulate in the brain. By binding to this specific epitope on the plaques, donanemab initiates their clearance.This binding activates microglial cells, the brain's resident immune cells, which then engulf and remove the plaques from the neuronal environment (see Figure 1). The reduction in amyloid plaque deposition is believed to slow the progression of Alzheimer's disease by limiting the toxic effects associated with plaque accumulation.At the molecular level, the clearance of plaques may help resolve synaptic dysfunction and prevent further damage to neuroplasticity—both of which contribute significantly to cognitive decline in AD. Additionally, at the genetic and biochemical level, donanemab may influence downstream pathways related to amyloid precursor protein (APP) metabolism. This can potentially disrupt the amyloid cascade, reducing tau hyperphosphorylation and the formation of neurofibrillary tangles—another
hallmark of AD pathology.By reducing amyloid levels throughout the brain, donanemab not only decreases neurotoxicity but also may help lessen inflammation triggered by plaque buildup. This process can safeguard surrounding neurons, potentially preserve cognitive function, and, in some cases, prevent or delay further mental deterioration.Moreover, lowering the amyloid burden may contribute to the stabilization or restoration of

synapticfunction,which is critical for memory, learning, and other cognitiveabilities.Donanemab is intended for use in individuals experiencing early symptoms of Alzheimer's disease, where intervention may have the most meaningful impact.

Clinical trials:-

Phase I Trials

The primary goal of Phase I clinical studies was to evaluate the safety, tolerability, pharmacokinetic profile, and initial therapeutic impact of Donanemab in humans. These trials included a small cohort of healthy volunteers along with patients in the early stages of Alzheimer's disease (AD). Various dose combinations were administered to understand tolerance levels. The findings indicated that Donanemab was generally well tolerated across different dosages. Some participants experienced adverse events, notably infusion-related reactions and amyloid-related imaging abnormalities (ARIA). Additionally, early observations noted a reduction in amyloid-beta (Aβ) plaques in the brain.

Phase II Trials

The TRAILBLAZER-ALZ Phase II trial was designed to further examine the efficacy and side effect profile of Donanemab in a larger group of patients with early-stage AD. This randomized, double-blind, placebo-controlled study involved approximately 272 participants. Donanemab was initially administered at 700 mg for the first three doses, followed by 1400 mg in subsequent infusions. PET imaging confirmed a significant reduction in Aβ plaque levels. Moreover, patients treated with Donanemab demonstrated improved cognitive performance, as assessed by scales such as the integrated Alzheimer's Disease Rating Scale (iADRS) and the Clinical Dementia Rating–Sum of Boxes (CDR-SB). ARIA-related side effects were managed through dose adjustments and careful monitoring.

Phase III Trials

The TRAILBLAZER-ALZ 2 Phase III trial (NCT04437511) aimed to validate Donanemab's effectiveness across a larger and more diverse patient population with early symptomatic AD. This multicenter, randomized, double-blind, placebo-controlled study enrolled approximately 1,736 participants. The dosing regimen resembled that used in Phase II but was adjusted based on individual patient responses. The results demonstrated a continued

reduction in Aβ plaque levels, along with noticeable improvements in cognitive functionand daily living abilities. At the one-year mark, nearly 50% of participants showed no further clinical decline, increasing to 69% by 18 months. The overall findings supported a positive benefit-risk profile, reinforcing Donanemab's potential as a disease-modifying therapy for Alzheimer's disease.

Current Clinical Trials of Donanemab

TRAILBLAZER-ALZ 3

This ongoing Phase 3 clinical trial investigates whether Donanemab can prevent cognitive decline in individuals at high risk of Alzheimer's disease who have not yet shown symptoms. Participants receive either Donanemab or a placebo over a 3.5-year period, with regular monitoring of cognitive performance.

Phase: 3

Objective: To determine if Donanemab can delay or prevent the onset of symptomatic Alzheimer's disease in asymptomatic individuals who are amyloid-positive.

Design: A randomized, placebo-controlled trial with a treatment duration of up to 3.5 years.

Participants: Around 3,300 cognitively unimpaired individuals, aged 55–80, selected for elevated plasma p-tau217 levels, indicating early amyloid and tau buildup.

Primary Outcome: Time until clinical progression, assessed through changes in Clinical Dementia Rating – Global Score (CDR-GS).

TRAILBLAZER-ALZ 4

This Phase 3 study directly compares Donanemab with Aducanumab to evaluate their effectiveness in clearing amyloid plaques in patients with early symptomatic Alzheimer's disease.

Objective: To assess and compare the amyloid plaque reduction achieved by Donanemab versus Aducanumab.

Design: A randomized, active-controlled trial involving patients with early-stage Alzheimer's disease.

Duration: 6 months.

Key Findings:After 6 months, 37.9% of participants treated with Donanemab showed significant reduction in amyloid plaque levels (defined as <24.1 centiloids), compared to only 1.6% in the Aducanumab group.

Conclusion: The study provided the first head-to-head comparison, demonstrating Donanemab's superior ability to remove amyloid plaques over Aducanumab, suggesting its greater therapeutic potential in early Alzheimer's treatment.

TRAILBLAZER-ALZ 5

This ongoing Phase 3 trial is designed to evaluate the effectiveness and safety of Donanemab in patients with early symptomatic Alzheimer's disease, particularly those with confirmed amyloid plaques and varying degrees of tau pathology.

Objective: To determine if Donanemab can slow down cognitive and functional deterioration in early Alzheimer's.

Design: A randomized, double-blind, placebo-controlled trial with a 1:1 treatment allocation.

Participants: Approximately 1,500 individuals diagnosed with prodromal Alzheimer's or mild dementia due to Alzheimer's.
Treatment Duration: Up to 93 weeks, including initial screening and follow-up periods.

TRAILBLAZER-ALZ 6

This Phase 3b study focuses on evaluating the safety and efficacy of different dosing schedules of Donanemab in patients with early Alzheimer's disease, with particular attention to ARIA-E (Amyloid-Related Imaging Abnormalities with edema or effusion), a known side effect.
Objective: To compare how different Donanemab dosing strategies influence the rate and severity of ARIA-E.
Design: A multicenter, randomized, double-blind trial including 843 participants aged 60–85, all diagnosed with early symptomatic Alzheimer's disease and confirmed amyloid positivity via PET scans. Treatment Groups: Participants were divided into four arms—one receiving the standard dose and the others receiving modified titration regimens.
Duration: 76 weeks of double-blind treatment. Key Findings:Participants in the enhanced titration group had fewer moderate to severe ARIA-E events compared to the standard dosing group.
There was a 41% relative risk reduction in ARIA-E incidence with enhanced titration (13.7%) compared to the standard regimen (23.7%) at 24 weeks.

Comparison of Donanemab, Lecanemab, and Aducanumab: Efficacy and Safety:-

Donanemab, lecanemab, and aducanumab are monoclonal antibodies developed to target beta-amyloid plaques in Alzheimer's disease, but they differ significantly in their mechanisms, therapeutic outcomes, and safety profiles. Donanemab specifically binds to a modified form of beta-amyloid known as N3pG. In the TRAILBLAZER-ALZ 2 trial, it demonstrated a 32% reduction in cognitive decline, with some patients—especially those with low to moderate tau burden—showing no further progression of the disease. Lecanemab, which targets soluble amyloid protofibrils, showed a 27% slowing of cognitive decline in the CLARITY-AD study. Aducanumab, which targets aggregated amyloid, has produced inconsistent clinical benefits, and its ability to halt disease progression remains unconfirmed. In terms of safety, the incidence of amyloid-related imaging abnormalities (ARIA) varies among the three:
Donanemab: ARIA was reported in about 27.3% of patients, primarily in the form of ARIA-E (edema) and ARIA-H (microhemorrhage).
Lecanemab: Demonstrated a lower ARIA incidence (12.6%), suggesting a better safety profile.
Aducanumab: Showed the highest ARIA rate, affecting around 41% of treated individuals.
All three therapies require regular MRI monitoring to manage ARIA risk and can cause infusion-related reactions. Donanemab and aducanumab are administered via intravenous infusions every 4 weeks, whereas lecanemab is given biweekly. Donanemab is particularly promising due to its potential not only to slow down but possibly halt disease progression in selected early-stage patients. However, due to the associated risks, careful patient screening and close monitoring are essential. Despite their comparable treatment costs, these drugs differ in dosing schedules, efficacy, and safety, making individualized patient care critical in therapy selection.

Comparison With Existing Treatments

Donanemab offers a novel and promising approach compared to traditional Alzheimer's treatments such as cholinesterase inhibitors and NMDA receptor antagonists. Cholinesterase inhibitors like donepezil, rivastigmine, and galantamine function by inhibiting the breakdown of acetylcholine, a neurotransmitter essential for memory andcognition. While these drugs can temporarily improve cognitive symptoms, their effectiveness is typically limited to a duration of 6 to 12 months. They do not impact the underlying disease process and often come with side effects such as nausea, vomiting, diarrhea, and fatigue. Their benefits tend to diminish in the moderate to severe stages of Alzheimer's disease. Memantine, an NMDA receptor antagonist, works by modulating glutamate activity in the brain. Although it provides symptomatic relief and may modestly delay cognitive decline in some patients, its effects are generally short-lived, and side effects like dizziness, confusion, and headache may limit its use. In contrast, donanemab represents a disease-modifying therapy. It targets N3pG-modified beta-amyloid plaques, contributing to the clearance of amyloid buildup and leading to a 32% reduction in cognitive decline among early-stage Alzheimer's patients. Moreover, clinical trials have shown that it may halt disease progression in a subset of patients, a capability not seen with current symptomatic treatments. Though associated risks such as amyloid-related imaging abnormalities (ARIA) and infusion reactions must be managed, donanemab's ability to alter the course of the disease sets it apart from traditional medications. Other amyloid-targeting therapies like lecanemab and aducanumab also attempt to change the disease trajectory. Lecanemab, which binds to amyloid protofibrils, has shown a 27% slowing of cognitive decline but does not halt disease progression. Aducanumab, despite its approval for reducing amyloid burden, has shown inconsistent clinical results, with varying impacts on cognitive outcomes. All three anti-amyloid therapies (donanemab, lecanemab, aducanumab) present safety concerns like ARIA and require regular MRI monitoring. However, donanemab's targeted mechanism and stronger clinical outcomes may make it a more promising option for early intervention in Alzheimer's disease. It signifies a potential shift from symptomatic relief to slowing or possibly preventing disease

Conclusion :-

Donanemab represents a significant advancement in the therapeutic management of Alzheimer's disease by directly targeting a key pathological hallmark—amyloid-beta plaques. Its demonstrated efficacy in slowing disease progression, particularly in patients with early symptoms, marks a turning point in disease-modifying strategies. However, the associated risk of ARIA and intravenous administration pose challenges that warrant further innovation. Ongoing studies into optimized dosing, delivery methods, and long-term safety are essential for enhancing its clinical utility and accessibility. The development of Donanemab underscores the potential of targeted immunotherapy in addressing neurodegenerative diseases.

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