***Review Article***

**TARGETING AMYLOID- LECANEMAB’S ROLE IN ALZHEIMER’S DISEASE MANAGEMENT: A COMPREHENSIVE REVIEW**

**ABSTRACT:**

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that affects the patient’s quality of life. The current regime of drugs only halts the symptoms of the disease, and the underlying pathology remains untouched; thus, there is progressive deterioration due to the intact pathology. Various drugs are being researched to address the complex neuropathology of AD. The FDA has approved lecanemab, which has shown considerable efficacy in reducing Aβ plaque, thereby addressing the pathology of the monoclonal antibodies being explored for AD, lecanemab shown higher selectivity towards Aβ and better efficacy in clinical improvement.

This study offers a comprehensive overview of the efficacy and safety of lecanemab, a monoclonal antibody, focusing on its binding properties and clinical trial results. Lecanemab’s unique binding profile, with a strong affinity for toxic Aβ protofibrils, sets it apart from other monoclonal antibodies. Clinical trials have shown promising results, including reductions in amyloid burden, improvements in cognitive measures, and a reduction in the rate of cognitive decline.

This review article aims to provide a comprehensive overview of Alzheimer’s disease, focusing on its epidemiology, risk factors, pathophysiology, and the emerging role of lecanemab as a potential disease-modifying therapy. By comparing lecanemab with existing symptomatic treatments that primarily address symptoms rather than underlying pathology, this review emphasizes the importance of targeting the fundamental mechanisms of AD for improved patient outcomes. Furthermore, it underscores the necessity for continued research to refine treatment strategies and enhance our understanding of this complex disease to better serve affected individuals and their families.

**INTRODUCTION:**

More than 50 million people worldwide suffer from Alzheimer’s disease (AD), a neurodegenerative condition marked by a persistent or progressive decline in cognitive function. In 2020 and 2021, it was formally ranked as the seventh most common cause of death. The most frequent cause of dementia is Alzheimer’s disease. In 2019, Tiwari et al **[1]**. Early signs of the condition include mood swings, decreased judgement, linguistic problems, recent memory loss, and a gradual shift in personality. The person fails to learn new information and recall (encoding, storage, and recall) over its unrelentingly progressive path. In addition to developing sphincteric incontinence and severe motor weakness, the person’s behavioural issues of wandering, anger, hostility, and bewilderment worsen, and they end up bedridden and completely dependent on everyday tasks **[2].** AD throws a great deal of strain on the family and has a significant impact on caregivers. Age is a significant risk factor; in the 65–69 age range, up to 10% of people get AD, while in the 85+ age range, over 50% of people have AD **[3],[4].** The Mini-Mental Scale Examination (MMSE) shows a loss of about 3.5 points every year. According to the theory, AD has a very long preclinical phase known as mild cognitive impairment (MCI), during which time the hallmark neuropathological alterations gradually but steadily accumulate and cause memory loss. There are two forms of MCI: The majority of people with amnestic MCI go on to develop full-blown AD. Non-amnestic MCI is characterized by a deterioration in non-memory cognitive abilities like language, executive function, and spatial. Amnestic MCI is characterized by memory impairment with intact cognitive skills in other domains. AD is separated into phases:

**Stage 1:** preclinical Alzheimer’s: There are no outward signs of the disease, but years before cognitive impairment, brain abnormalities, including tau tangles and amyloid plaques, start to appear.

**Stage 2:** Mild cognitive impairment (MCI) manifests as early memory and cognitive problems that do not significantly impact day-to-day functioning. Some people develop Alzheimer’s disease.

**Stage 3:** moderate Alzheimer’s disease: significant disorientation and memory loss appear, affecting day-to-day activities including money management and recalling recent events.

**Stage 4:** mild Alzheimer’s disease: people experience a substantial cognitive deterioration that makes day-to-day tasks difficult. Significant memory loss, uncertainty about time and location, trouble identifying loved ones, and language issues are some of the symptoms. There may be behavioural changes that call for help with personal care, like anxiety and mood swings.

**Stage 5:** Severe Alzheimer’s disease: cognitive and physical capacities significantly deteriorate in this last stage. People need full-time care when they lose the ability to recognize and converse with family members. Additionally, they can have trouble swallowing and moving around, which makes them more susceptible to infections and other health problems.

**Alzheimer’s disease staging:**

**Figure 1:** Staging of Alzheimer’s disease.

AD throws a great deal of strain on the family and has a significant impact on carers. Age is a significant risk factor; in the 65–69 age range, up to 10% of people get AD, while in the 85+ age range, over 50% of people have AD **[5].**

**THE CAUSES AND CONTRIBUTING VARIABLES OF ALZHEIMER’S DISEASE**

Examining the genetic, environmental, behavioural, and acquired risk factors that influence the development and course of Alzheimer’s disease is essential to comprehending its aetiology.

**Genetic components**

1. **Deterministic genes:** Alzheimer’s disease is directly caused by some genetic alterations, especially in cases that start early in families. Important genes consist of:

* **Amyloid precursor protein (APP):** This protein is mutated to produce more amyloid-beta peptides, which aid in the development of plaque in the brain.
* **Presenilin 1 (PS1) and presenilin 2 (PS2):** The enzymatic digestion of APP is mediated by the genes presenilin 1 (PS1) and presenilin 2 (PS2). About 5% of familial AD is caused by mutations in these genes, which also result in increased production of amyloid beta (Cleveland clinic).

1. **Risk genes:**

* **Apolipoprotein E (ApoE):**  is the most prominent risk gene; in particular, the e4 allele considerably increases the chance of developing AD. The disease is three times more likely to strike someone with one e4 allele and 6.5 times more likely to strike someone with two e4 alleles. The ApoE €4 allele is present in at least one copy in almost 50% of AD patients.

**Risk factors that are acquired:**

1. **Cerebrovascular diseases:** Cognitive decline is significantly influenced by vascular health. Circumstances like:

**• Ischaemic infarcts:** dementia may result from both minor and major infarcts.

**• Vasculopathies:** It is well recognised that alterations in blood vessel and white matter integrity raise the risk of AD. According to postmortem investigations, vascular pathology is highly prevalent in AD patients, suggesting a possible link between amyloid buildup and cerebral health.

According to the “double-stroke” theory, vascular risk factors cause neuronal injury, decreased cerebral blood flow, and blood-brain barrier dysfunction. Neurodegeneration is accelerated by this process, which also encourages tau hyperphosphorylation and amyloid beta buildup (Love and Miners, 2016) **[6].**

1. **Hypertension:** A higher risk of AD is associated with elevated blood pressure. According to longitudinal research, high blood pressure, especially in middle age, has a detrimental impact on cognitive function in later life. According to Skoog and Gustafson (2006), may result in:

**•** Alterations to the vascular wall that cause ischaemia and damage to neurones;

**•** Increased expression and buildup of amyloid-beta and amyloid precursor protein (APP) **[7].**

1. **Type II Diabetes:** There is ample evidence linking this illness to AD. Among the possible mechanisms are:

• **Insulin resistance:** Enzymes involved in the synthesis of amyloid beta may become more active when insulin signalling is compromised.

**• Chronic inflammation:** Vascular inflammation and damage brought on by diabetes contribute to neurodegenerative processes.

**• Advanced glycation end products (AGEs):** These substances, which are produced when blood glucose levels are elevated, have the potential to induce amyloid-beta deposition and cause neuronal death (Li et al., 2015) **[8].**

* **Obesity:** Obesity plays a complicated and age-dependent role in AD. According to certain research.

**• Obesity in middle age**: Because of its inflammatory effects and metabolic instability, it is linked to an increased risk of AD.

 . **• Obesity in later life:** Findings vary; some research suggests that it may even have an inverse relationship with the risk of dementia, possibly as a result of confounding health conditions in the elderly (Anstey et al., 2011) **[9].**

1. **Dyslipidemia:** It has been suggested that high cholesterol is a risk factor for AD. The following are associated with hypercholesterolaemia is linked to:

• Increased brain amyloid beta deposition,compromised blood-brain barrier integrity, facilitating, Neuroinflammation and cognitive decline (Xue Shan et al., 2016). **[10]**

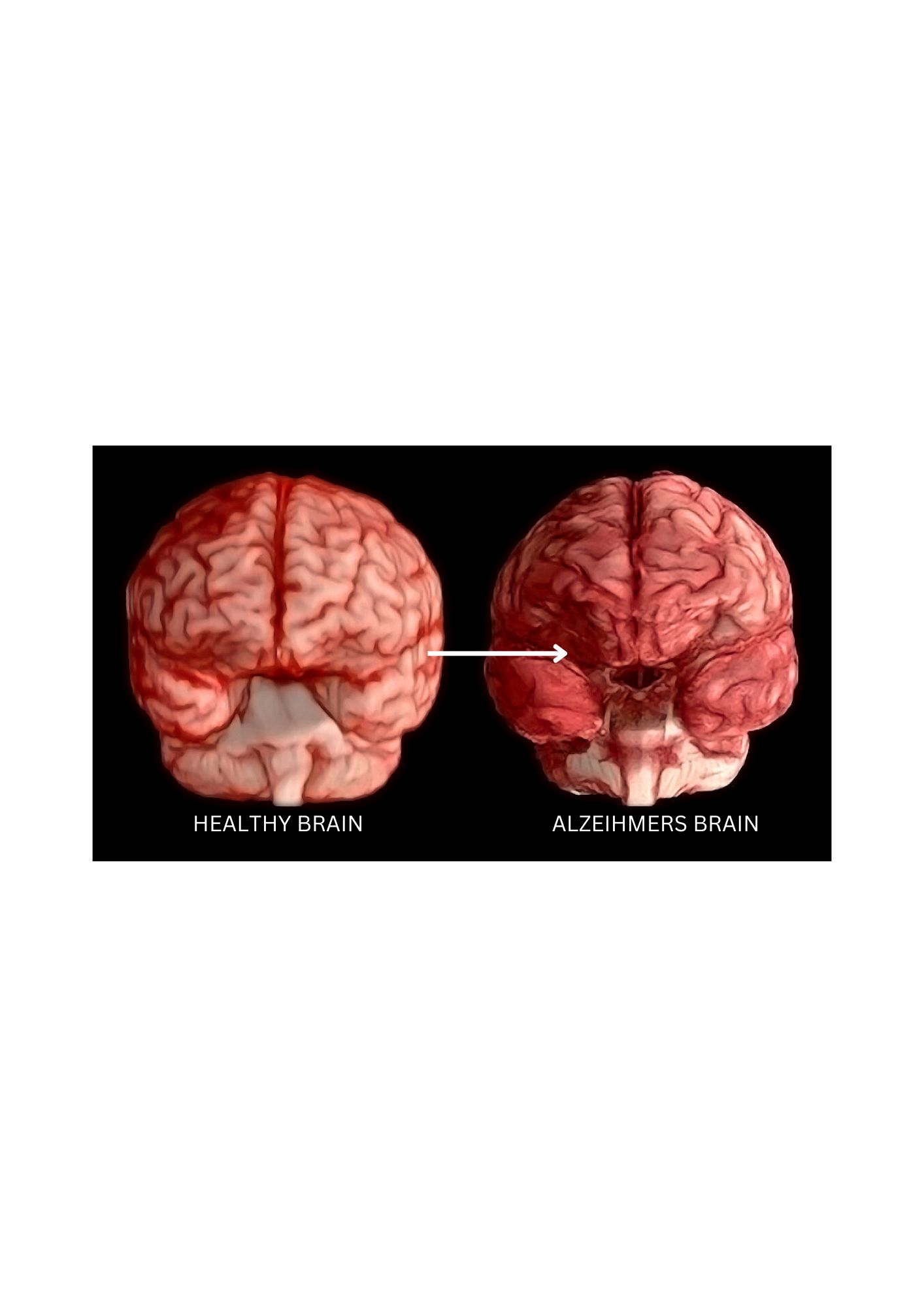
**Lifestyle and environmental influences**

* **Age:** The biggest risk factor for AD that cannot be changed. Nearly one-third of people over 85 will get Alzheimer’s disease, and the risk doubles every five years after age 65 (Alzheimer’s association).
* **Family history:** An individual’s risk is increased if they have a family history of AD, especially if several relatives are impacted.
* **Cardiovascular health:** Disorders that impair cerebral blood flow, including hypertension, diabetes, and hyperlipidaemia, increase the risk of AD.
* **Head injury:** A higher risk of developing AD has been linked to severe brain traumas and repeated concussions.
* **Lifestyle factors**: The risk of AD is greatly influenced by modifiable lifestyle choices.
* **Physical inactivity:** higher risk is associated with sedentary lifestyles.
* **Smoking:** Because tobacco affects inflammation and vascular health, it is associated with an increased risk of AD.
* **Diet:** Unhealthy eating patterns increase risk, especially when they include a lot of sugar and saturated fat. On the other hand, diets high in omega-3 fatty acids and antioxidants may provide preventive advantages.**[11].**

**Cognitive and behavioural aspects**

* **Cognitive engagement:** Engaging in mentally challenging activities throughout one’s life can improve cognitive reserve and possibly postpone the onset of AD symptoms. Maintaining cognitive function may be aided by learning and solving problems.

The risk of cognitive decline may be decreased by actively participating in social and communal activities, which promote mental health. Better cognitive outcomes are linked to strong social networks[**12**].



**Figure 2:** Demonstration of Healthy Individual Brain and Alzheimer’s disease Brain

**EPIDEMIOLOGY OF ALZHEIMER DISEASE**

The primary characteristic of dementia, a multifaceted illness, is the steady decline of cognitive abilities across multiple domains, which hinders daily functioning in social, physical, and occupational domains **[13].** Currently, dementia affects over 35.6 million individuals globally, with 7.7 million new cases recorded each year **[14].** According to recent projections, the “baby boomer” phenomenon will cause Europe’s population to increase by 87% between 2010 and 2050 **[15].** Alzheimer’s disease (AD) is the most prevalent neurodegenerative disease, accounting for 60–80% of dementia cases reported. It significantly burdens national and worldwide healthcare systems **[16].**

Unlike AD, which has increased by 68% in the past ten years, other health disorders, such as cardiovascular disease, have shown a decline in the modern age **[17].** According to studies on AD, the incidence rate is 6.3 per 100,000 and the yearly prevalence is roughly 24.2 per 100,000 among those aged 45–64 **[18]**. Nonetheless, the disease is much more common in people over 65, and the likelihood of developing AD increases exponentially. **[19].**

**LECANEMAB**

IgG1 monoclonal antibody lecanemab, sometimes referred to as BAN2401 or Leqembi, is a drug intended to bind to and interact with soluble amyloid-beta clumps, specifically oligomers and protofibrils**[20].** At Bio Arctic Neuroscience, where this drug was first created, it was discovered that the Amyloid Precursor Protein (APP) has a mutation **[21]**. People with the mutation and Alzheimer’s disease have high levels of amyloid-protofibrils and no amyloid plaques **[22].** Targeting APP (Amyloid Precursor Protein) with the Arctic mutation E693G, lecanemab is a humanized IgG1 monoclonal antibody that has been demonstrated to primarily bind to soluble amyloid beta protofibrils **[23].**Several preclinical studies have demonstrated that lecanemab preferentially reduces amyloid beta protofibrils and pathogenic amyloid beta levels in the brains of mice genetically engineered to produce human amyloid precursor protein with two specific mutations: Swedish (KM670/67INL) and Arctic (E693G) **[24]**.Based on the findings of first- and second-phase clinical trials, lecanemab has garnered a lot of attention as a possible treatment for AD and has spurred additional research to ascertain its effectiveness **[25].** And positive preclinical results. Interestingly, it has recently been demonstrated that lecanemab lowers blood levels of P-Tau181**[26]**. This discovery, together with the data from the first and second phases, motivated the DINA trial unit team to investigate the first double adaptive tau-amyloid-beta treatment, which included combining Lecanemab with Eisai’s anti-tau antibody E2814 **[27]**.People with a family history of AD due to a particular inherited genetic variation (in genes called APP, presenilin 1, and presenilin 2) are given a test to check for the presence of abnormal protein deposits in the brain called amyloid-cognitive symptoms as part of a novel prevention clinical trial called DIANTU**[28]**. Between 1% and 5% of all cases of Alzheimer’s disease are caused by this kind of genetic variation **[29]**. To find out how well lecanemab affected cognition in early Alzheimer’s disease, a phase III randomized, placebo-controlled, double-blind study compared it to a placebo **[30].**

Among these Mabs, lecanemab exhibits encouraging outcomes when used to treat AD. It functions by lessening the buildup of amyloid beta in the brain, which is a defining feature of the illness. Cognitive decline has improved as a result of this decrease in amyloid beta, and the occurrence of the adverse consequence known as ARIA has also been comparatively rare. According to research, lecanemab, when given by intravenous infusion once every two weeks at a dosage of 10 mg/kg, is safe and has a minor therapeutic effect. To prove lecanemab’s safety and effectiveness, more research is required **[31]**.

**MOA OF LECANEMAB**

Lecanemab is a monoclonal antibody developed to treat Alzheimer’s disease. The major mechanism of action (MOA) targets amyloid-beta (Aβ) protofibrils, which are linked to Alzheimer’s disease.

1. **Targeting Aβ protofibrils:**

 Alzheimer’s disease is distinguished by the presence of amyloid plaques in the brain, which are clumps of misfolded amyloid beta peptides. These plaques are thought to affect cell function and cause neurodegeneration.

 Lecanemab specifically targets soluble Aβ protofibrils, which are intermediate-sized aggregates generated during the transition from monomeric Aβ to insoluble amyloid plaques. Proteins are regarded as particularly hazardous since they are soluble and can alter synaptic function, resulting in cognitive impairment and neuronal damage **[32].**

1. **Reduction of Amyloid Plaques:**

Lecanemab reduces amyloid plaques by binding to Aβ protofibrils and preventing further aggregation.

Lecanemab binds to Aβ protofibrils, promoting their clearance by the brain’s immune system. This procedure is expected to lessen the total load of amyloid plaques in the brain.

 Lecanemab may block the seeding and spreading of new amyloid plaques by lowering the number of protofibrils, potentially reducing disease progression.

1. **Microglial activation and clearance:**

 Lecanemab binds to protofibrils, allowing microglia, the brain’s immune cells, to recognize them more easily.

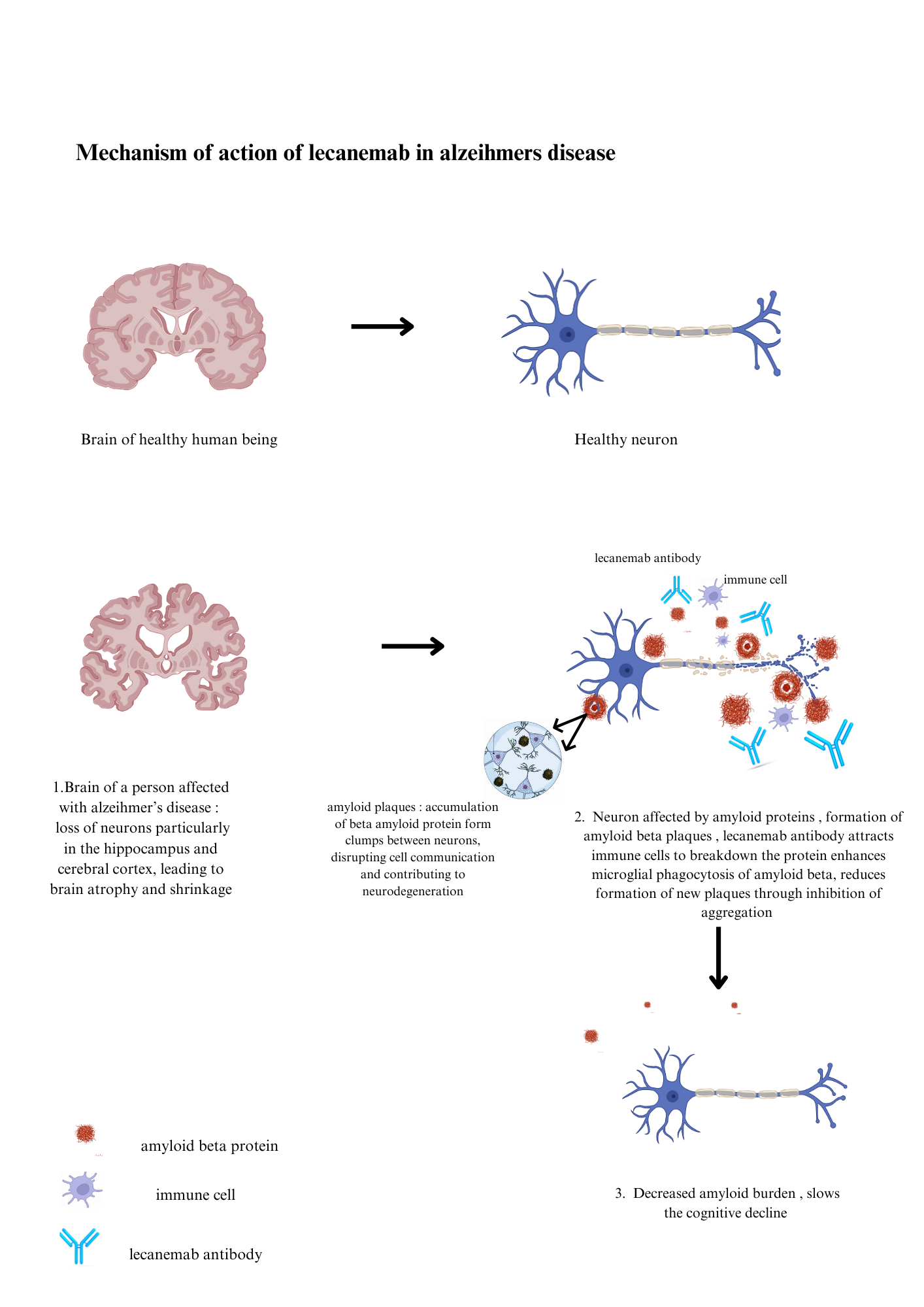
Microglia help remove cellular waste and misfolded proteins. Lecanemab-bound protofibrils activate microglia, which engulf and degrade Aβ aggregates, removing the dangerous substance from the brain. Immune-mediated clearance reduces neuroinflammation caused by amyloid accumulation and may have a neuroprotective impact.

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1. **Impact on Disease Progression:**

By targeting amyloid pathology, lecanemab hopes to alter the underlying disease process rather than just alleviating symptoms.

The medicine is used in the early stages of Alzheimer’s disease, such as moderate cognitive impairment (MCI) or mild dementia caused by Alzheimer’s, when amyloid pathology is still building and intervention may be most beneficial **[33].**

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**Figure 3:** Mechanism of Action of Lecanemab in Alzheimer’s disease

**PHARMACOKINETICS:**

1. **Absorption and Distribution**: Intravenous (IV) administration of lecanemab ensures full bioavailability. Lecanemab has a limited diffusion outside of the vascular compartment, as evidenced by its distribution capacity of about 3.8 liters.
2. **Metabolism:** Lecanemab is a monoclonal antibody that, like natural immunoglobulins, is broken down by proteolysis into smaller peptides and amino acids. It is not metabolized by the system of cytochrome P450 enzymes**.**
3. **Elimination:** Lecanemab has an elimination half-life of roughly 5 to 7 days, which permits dosing every two weeks. Since its excretion is not heavily dependent on renal excretion, clearance is around 0.225 L/day, and no dose modification is necessary for renal or hepatic impairment **[34]**.
4. **Special Populations:** Mild to moderate renal or hepatic impairment does not substantially change the pharmacokinetics in Alzheimer's patients. Pharmacokinetics have not been found to alter based on gender **[35].**

**PHARMACODYNAMICS**

Lecanemab may decrease the progression of Alzheimer’s disease and enhance cognitive performance in those who are affected by it by lowering Aβ aggregation and toxicity **[36]** Lecanemab may be a useful treatment for Alzheimer’s disease since it targets and removes harmful Aβ oligomers from the brain, according to its overall pharmacodynamics **[37]**. To completely understand lecanemab’s therapeutic potential in the treatment of this debilitating neurological disease, more clinical research is required **[38].**

**CLINICAL EVIDENCE FOR THE USE OF LECANEMAB**

**Preclinical**

In 2001, Nilsberth et al.identified preclinical Aβ protofibrils as a pathogenic mechanism for AD after observing a unique APP mutation called "Arctic" that accelerated the development of Aβ protofibrils and caused early-onset AD symptoms in mutation carriers**[39]**. According to an in vivo study conducted in transgenic mice that expressed the Swedish and Arctic APP mutations (also known as "ArcSwe"), mAb158, which was initially created to detect Aβ protofibrils, decreased both soluble and insoluble Aβ plaques when given early in the course of the disease. The humanized BAN2401 was developed as a result of research on human post-mortem AD brains, which revealed that mAb158 bound to comparable soluble Aβ protofibrils (about 80–500 kDa) in the human samples **[40].**

**Phase I**

In order to evaluate lecanemab’s safety, PK, and impact on plasma and CSF biomarkers, the phase I clinical trial (NCT01230853) recruited 80 subjects [20]. The MMSE scores of 16–28 and the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer’s Disease and Related Dementias Association (NINCDS-ADRDA) criteria indicated that the eligible participants had mild to moderate AD. Six lecanemab and two placebos per cohort were randomly assigned to single and multiple ascending dose arms. 0.1, 0.3, 1, 3, 10, and 15 mg/kg were included in the SAD trial, and 0.3, 1, and 3 mg/kg were included in the MAD study. Given every four weeks and every two weeks at a dose of 10 mg/kg. SAD And MAD were performed with staggered parallel cohorts; MAD was initiated once the dose was established as well tolerated inthe SAD cohort. Lecanemab was well tolerated in both dosage arms. PK analyses indicated lecanemab had a dose-proportional response and a 7-day serum half-life with doses ≥10 mg/kg. There was no observed ARIA-E; ARIA-H was observed in two cases in the SAD cohorts (one symptomatic) and six cases (all without symptoms) in the MAD cohorts (with one being placebo). Biomarker changes observed were limited to a mild increase in plasma Aβ1–40 **[41].**

**Phase II**

Phase II The phase IIb trial of lecanemab (NCT01767311) was an 18-month study that enrolled 856 subjects to determine the dose and efficacy of the treatment **[42].** Participant eligibility Required Aβ pathology confirmed by PET or CSF Aβ1-42 measurement, an MMSE ≥22 (22–28 in participating EU nations), and objective memory impairment (Weschler Memory Scale IV–Logical Memory II [WMS-IV LMII]) criteria. A unique Bayesian adaptive dose-finding trial design was used for the first 12 months to assess the primary endpoint, the change from baseline on the AD Composite Score (ADCOMS). For a dose arm to be successful at the 12-month objective, it had to have an 80% chance of decreasing the decline on the ADCOMS by 25% more than a placebo. 196 of the 854 participants in the trial were randomized to receive a placebo (n = 56) and five distinct dosage arms (2.5, 5, and 10 mg/kg every two weeks, and 5 and 10 mg/kg every month, n = 28 each cohort). Following that, each cohort's ADCOMS performance was used to randomly assign each of the 50 participants to the dose arms. At 12 months, the trial's main goal was not met, even though the biweekly dose of 10 mg/kg had a 64% chance of delaying the fall in ADCOMS by 25% more than the placebo. Up until month 18, the trial was double-blind.

On the ADCOMS and ADAS-Cog, frequentist analyses showed statistically significant differences favouring lecanemab. In 81% of participants, amyloid PET showed Aβ plaque reduction below the detection threshold. The combined biweekly and monthly 10 mg/kg lecanemab arm had increased Aβ1-42 and reduced P-tau at 18 months compared with placebo in an optional substudy of CSF biomarkers. Because APOE ε4 carriers are the most at risk for ARIA, a significant change to the trial required that they be removed from the 10 mg/kg biweekly arm as directed by a regulatory body. The trial's high-dose arm had fewer APOE ε4 allele carriers as a result of this adjustment. Infusion responses were the most frequent adverse effects (AEs), other from ARIA which responded to prophylactics or treatment and were often mild or moderate **[43].**

**Phase III**

 1795 patients were recruited for "CLARITY AD" (NCT03887455), and they were randomized 1:1 to either the placebo arm (n = 897) or the 10 mg/kg biweekly Lecanemab arm (n = 898**).**Age (50–90 years), a diagnosis of mild AD or MCI (National Institute on Aging–Alzheimer’s Association [NIA-AA] criteria), a 1 SD decline in objective episodic memory below the age-adjusted mean (WMS-IV LMII), and Aβ positivity by PET or CSF Aβ1–42 measurement were the criteria used to determine eligibility. The change from baseline on the CDR-SB at 18 months was the main endpoint for CLARITY AD. In comparison to a placebo, lecanemab delayed the decline on the CDR-SB by 0.45 points (+1.21point change) (+1.66point change). Other cognitive measures in the lecanemab arm (ADAS-Cog, ADCOMS, ADCS-ADL-MCI) had significantly slower decline than placebo at 18 months. Amyloid PET plaque levels were reduced on lecanemab (−55.48 centiloid change) versus placebo (+3.64 centiloid change). All CSF and plasma biomarkers favoured lecanemab over placebo except for neuroflament light (NfL), which showed no Drug-placebo difference. Infusion-related reactions (26.4%), ARIA-H (17.3%), and ARIA-E (12.6%) were the most com-Mon AEs in the lecanemab dosage arm. Non-carriers of The APOE ε4 allele in the lecanemab arm had the lowest Incidence of ARIA-H (11.9%) and ARIA-E (5.4%); ε4 het-Erozygotes had a higher incidence of both (ARIA-H: 14%; ARIA-E: 10.9%). APOE ε4 homozygotes had an incidence of ARIA-H and ARIA-E in 39% and 32.6%, respectively. Because lecanemab's Aβ decrease in the phase IIb trial was thought to be a relatively good indicator of clinical effect, the FDA gave it fast approval. Based on the findings of CLARITY AD, the FDA gave lecanemab standard approval **[44].**

**LECANEMAB'S EFFECTIVENESS AND SAFETY IN AD**

Lecanemab, an anti-amyloid monoclonal antibody, has shown promise in treating Alzheimer's disease (AD) by focusing on amyloid-beta (Aβ) plaques, which are a major feature of the disease. Depending on the stage of AD, its effectiveness varies; early-stage treatments have the strongest evidence.

**1. Alzheimer's disease in its early stages (mild AD and mild cognitive impairment)**

**Effectiveness:** In early-stage AD, lecanemab has shown notable effectiveness in reducing cognitive and functional deterioration, particularly in mild AD or moderate cognitive impairment (MCI). According to clinical research, including the Phase 3 Clarity AD trial, lecanemab-treated patients had a 27% lower rate of decline than placebo-treated patients, as determined by the Clinical Dementia Rating-Sum of Boxes (CDR**-**SB) **[45].**

**Mechanism:** When used early in the course of the disease, lecanemab is believed to be crucial in slowing the progression of the condition because it targets and reduces the accumulation of Aβ plaque **[46].**

**2. Alzheimer's disease that is moderate**

**Efficacy:** Since most studies focus on patients in the early stages of AD, there is little information available on lecanemab's effectiveness in this condition. According to the underlying mechanisms, amyloid-targeting therapies such as lecanemab may be less effective in moderate stages of neurodegeneration, when tau tangles and extensive brain cell loss are present in addition to amyloid plaques. Proof from Additional Anti-Amyloid Treatments: In moderate stages of AD, when interventions frequently fail to reverse significant neurodegeneration, similar amyloid-targeting therapies have demonstrated limited benefit **[47].**

**3. Alzheimer's disease that is severe**

**Efficacy:** Patients with severe AD are not usually tested for lecanemab. Because of the severe neurodegeneration and diminished significance of amyloid plaque as a determinant in the progression of the illness, anti-amyloid treatments are typically less successful in advanced stages of AD. As a result, early intervention is emphasized in current treatment guidelines and trials.

**Risk and Safety:** Lecanemab frequently causes amyloid-related imaging abnormalities (ARIA), including edema and microhemorrhages, particularly in patients with a higher amyloid burden, which is frequently seen in moderate-to-severe AD **[48].** The limited significance of amyloid-targeting medicines in later stages of AD is supported by this study, despite its focus on another anti-amyloid drug.

**RISKS AND ADVERSE EFFECTS RELATED TO LECANEMAB**

Evaluating possible adverse effects and medication risks is crucial while contemplating a course of treatment for any ailment. Better prognostic prognosis, patient compliance, and management are made possible by this understanding. Headaches, light-headedness, and nausea were the most frequent side effects linked to Lecanemab infusions. These side effects were more common in the higher-dose group and were typically mild to moderate in intensity **[49, 50].** Death was observed in 0.8% of the placebo group and 0.7% of lecanemab patients. Brain parenchymal edema, superficial siderosis, and cerebral micro haemorrhages are frequently linked to amyloid-related imaging abnormalities (ARIA)] **[50]**. Anti-Aβ antibodies, which may bind to cerebral amyloid antipathy (CAA) or increase CAA production, are frequently found to have this type of ARIA **[51]**. Higher medication dosages and the presence of the ApoE4 genotype were associated with a higher prevalence of ARIA in patients **[52].** Given that genetic investigations are rarely conducted in clinical practice before beginning treatment, it is alarming that patients who are ApoE4 carriers unexpectedly displayed improvement in cognitive deterioration **[53].** However, lecanemab may cause clinical deterioration in AD patients who are ApoE4 carriers.When compared to other medications used to treat AD, such as cholinesterase inhibitors (donepezil, galantamine, and rivastigmine), these side effects are specific to monoclonal antibodies**[54].**

In a phase 3 trial for preclinical AD patients who received solanezumab also experienced side effects like ARIA with microhemorrhages, hemosiderosis, or edema, and even aducanumab **[55]**. Overall, lecanemab's safety profile was favorable, and the Phase III trial revealed no new safety concerns. The findings indicate that lecanemab has a manageable safety profile and that the treatment's advantages outweigh its risks **[56].**

**COMPARISON WITH ALTERNATIVE THERAPIES FOR AD**

Cholinesterase inhibitors, which raise acetylcholine levels, are among the few known treatments for AD at the moment. These include galantamine, rivastigmine, and donepezil. Memantine, an NMDA receptor antagonist that controls glutamate activity, is the alternative. These medications do not alter the course of the disease; they merely relieve its symptoms **[57]**. Therefore, the alleviation is only momentary and disappears when the prescription is stopped because it offers no real benefit. There is no attention being paid to the main pathophysiology underlying AD. Conversely, lecanemab, which is currently FDA-approved, helps to reduce disease by addressing the main amyloid pathology in the brain, which delays cognitive loss and slows the progression of the disease. However, the patient not only experiences symptomatic relief, However, the primary pathology is being addressed in order to fully eradicate the illness **[58].**

**THE EFFECTIVENESS OF OTHER MONOCLONAL ANTI-AMYLOID Aβ ANTIBODY MEDICATIONS**

Two noteworthy phase III clinical trials, "ENGAGE" (NCT02477800) and "EMERGE" (NCT02484547), were conducted on aducanumab [24]. The outcomes of both trials were nearly identical to those of the placebo**.** Biogen after that due to interim post hoc assessments demonstrating futility, both studies were terminated. Additionally, the FDA continues to approve the drug June 2021 **[59].** However, there are serious doubts about its effectiveness and usefulness. In AD, gantenerumab has also demonstrated some promise. Doses as high as 1200 mg when given subcutaneously showed a significant decrease in Aβ in people with prodromal to mild AD once every four weeks **[60].** Phase III trials and additional research are needed to demonstrate its effectiveness and win FDA approval. In the EXPEDITION 1 and 2 phase 2 studies, solanezumab reduced beta-amyloid levels; however, this effect was limited to mild AD and did not ameliorate moderate AD. The outcomes were nearly identical to a placebo, even in patients with moderate AD **[61].** Even in EXPEDITION 3, the main goal of reducing cognitive decline was not achieved in a solanezumab Phase 3 trial that was started in a cohort of patients with moderate AD. Solanezumab was preferred in a number of secondary clinical endpoints, such as cognitive and functional assessments, but the benefit was essentially non-comparable **[62].**

**CONCLUSION**

Alzheimer’s disease possess a profound challenge to global health affecting millions of people worldwide and it significantly impacting families and caregivers. Examination of Lecanemab’s ability to bind, its effectiveness in clinical settings, and its safety record offers a positive outlook on its potential contribution to the therapy of Alzheimer’s disease (AD). Overall, although Lecanemab demonstrates potential in specifically targeting Aβ protofibrils and producing favorable clinical results, more investigation and a comprehensive evaluation of its safety and long-term efficacy are essential for determining its function in treating Alzheimer’s disease. The discourse surrounding Lecanemab highlights the necessity of a well-rounded comprehension of its ad-vantages and possible obstacles to guarantee informed decision-making in treating Alzheimer’s disease.The results of this study have the potential to inform clinical guidelines and benefit healthcare professionals, caregivers, and researchers in their efforts to improve the treatment of AD. This review is a crucial step in addressing the growing challenge of AD and enhancing the well-being of affected individuals and their families.While lecanemab presents a favourable safety profile, it is associated with amyloid-related imaging abnormalities (ARIA). Unlike symptomatic treatments, lecanemab addresses the disease’s underlying pathology, marking a significant advancement in AD therapy

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