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Review Article

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Lecanemab: A Recently Researched Drug for Treating Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a vastly operable neurological disease, that typically affects people over the age of 65. As individuals age, the number of neurons in their brains tends to decrease gradually in healthy individuals, but AD sufferers' brains exhibit a substantial rise in neuron death, frequently leading to a considerable decline in cognitive function. At this time, only postmortem brain biopsies can provide a conclusive diagnosis of AD by identifying extracellular amyloid beta plaques and intracellular hyperphosphorylated tau neurofibrillary tangles. In this review, lecanemab, a phase-three disease-modifying biologic therapy, is discussed along with its background and current clinical trials for AD. In recent years, researchers have developed monoclonal antibodies that can target and remove amyloid-beta proteins, which are believed to contribute to the development & progression of AD. These antibodies include drugs like Aducanumab, Bapineuzumab, Gantenerumab, Solanezumab, and Lecanemab. The idea behind these drugs is that a breakdown in the body's natural ability to clear amyloid-beta protein can contribute to the development of AD. Clinical studies have been carried out to test the effectiveness of these antibodies in treating AD. We concentrated on the topic of lecanemab effects on AD pathogenesis and clinical characteristics. The review offers potential support for using immunotherapy with mabs (lecanemab) in AD and analyses the clinical trial lessons learned to further research the beneficial and harmful effects of this on anti-amyloid beta AD.

1.1 Introduction

Alzheimer's disease is a progressive neurological condition caused by cell death. It reports the deposition of senile plaques and paired helical filaments (PHF) in the brain. Alois Alzheimer, a German psychiatric clinician and neuro-anatomist, is credited with the initial discovery of AD. He looked at the brain of a patient named Auguste D. through a microscope and found some unusual changes. These changes are known as the hallmarks of AD. After Dr. Alois Alzheimer's passing, more studies were conducted, and they started to stage AD. Pre-clinical, mild, moderate, moderately severe, severe, and extremely severe are the six stages. The deterioration of memory and cognitive function progressively and irreversibly is a characteristic feature of this condition, including the inability to carry out everyday routine chores, which is one of the symptoms. As of yet, there is no efficient way to reliably identify the diagnosis of AD without first doing a postmortem brain autopsy. These postmortem tissue samples show a variety of diseases, including brain shrinkage linked to the appearance of this condition, intracellular tau-tangles inclusive of hyperphosphorylated tau proteins, and Aβ peptides can aggregate outside the cell to form plaques [1,2,3]. The presence of these two proteins is a sign of AD, and leisure activity probably plays a significant role in the disease's pathologic development. AD comes in two different forms: early-onset and late-onset. The apolipoprotein E gene (APOE), and more specifically, the allele of the APOE gene, are thought to be hereditary risk factors for late-onset Alzheimer's disease[4,5]. The role of APOE is to control blood cholesterol levels[3]. People who carry this genotype typically experience the development of amyloid-beta before those who do not carry the allele [5,6]. There are two subcategories of early-onset Alzheimer's disease: usual and hereditary. The typical form of Alzheimer's disease that appears early in life develops in a manner that closely resembles the progression of late-onset Alzheimer's disease. Yet it developed in individuals who were younger than 65 years old. High temperatures affect 100 people globally who have a genetic form of Alzheimer's disease that developed at an early age, in which a particular gene causes the disease. Mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN-1), and presenilin 2 (PSEN-2) genes are specifically associated with early-onset Alzheimer's disease[4]. Individuals typically start exhibiting symptoms between the ages of 30 and 50. A family history increases the likelihood of both early-onset Alzheimer's disease subtypes. [7]. Acetylcholine-esterase inhibitors (AchEIs), like donepezil, galantamine, and rivastigmine, are now the only treatment option for AD. AchEIs have been linked to a phenomenon that momentarily slows AD progression [8]. Ach is not so effective in AD because there has been no significant alternation in the rate at which individuals with mild cognitive impairment progress to AD. It is uncertain whether AchEIs are beneficial in slowing the course of AD [8]. According to studies, only large doses of AchEIs are considerably helpful; nevertheless, the clinical use and usefulness of these drugs have been questioned due to the increased incidence of side effects linked to greater dosages and longer periods of administration [8.] Investigations into alternative treatments are being conducted due to the frequent side effects. APP is a protein that is found in many organs of the body. However, this protein can be broken down into smaller pieces called Aβ. This breakdown process involves two enzymes called beta-secretase and gamma-secretase, which work together in a complex [9]. The non-amyloidogenic pathway involves the cutting of APP by alpha-secretase activity at a point within the amyloid-beta sequence and then through gamma-secretase, producing a short peptide termed p3 with an unknown function. In brains with high levels of neuronal expression, APP is expressed at its maximum levels. The "amyloid cascade hypothesis" is the most widely held clarification explaining the Pathophysiology of AD [10,11]. According to this theory, tau tangles, neuronal atrophy, vasculopathy, senility, and memory loss are all side effects of amyloid-beta deposition, which is the underlying cause of AD pathogenesis. The two A-centric AD hypotheses mentioned above are currently being addressed by three key

treatment interventions: (i) lowering the production of amyloid beta; (ii) enhancing the elimination of amyloid beta; and (iii) a potential strategy to inhibit the aggregation of amyloid beta. Small-molecule medicines and immunotherapies are among the tactics investigated to eliminate amyloid-beta effectors [12,13]. In this article, we will explore the latest research on drugs and treatments that are being tested or have been approved by the US FDA to reduce the buildup of a protein called amyloid-beta in the brain. This will include both small molecules of medication and immunotherapies, and we will look at the most recent preclinical and clinical studies[10].

2. Recently researched drug to treated earlier Alzheimer's disease: Lecanemab

IgG1 monoclonal antibody lecanemab, also known as BAN2401 or Leqembi, is a medication that is designed to attach to and interact with clumps of amyloid-beta that are soluble, with a particular focus on oligomers and protofibrils [14]. The Amyloid Precursor Protein (APP) was found to have a mutation at Bio Arctic Neuroscience, where this medication was initially developed [15]. There are no amyloid plaques and large quantities of amyloid-protofibrils in people with the mutation and Alzheimer's disease [15]. Lecanemab is a humanized IgG1 monoclonal antibody that targets APP (Amyloid Precursor Protein) that carries the Arctic mutation E693G and has been shown to attach predominantly to soluble amyloid-beta protofibrils [16,17]. Lecanemab has been proven in several preclinical investigations to preferentially diminish amyloid-beta protofibrils and lower pathogenic amyloid-beta levels in the brains of mice that have been genetically modified to produce human amyloid precursor protein with two specific mutations, arctic (E693G) and Swedish (KM670/67INL) [18,19]. Lecanemab has attracted significant interest as a potential therapy for AD and has sparked more trials to determine its efficacy based on the results of first-phase and second-phase clinical trials [16,20] and favourable preclinical findings. It is interesting to note that lecanemab has recently been shown to reduce P-tau181 levels in the blood. The DINA trial unit team was inspired by this finding, along with the data from the first phase and second phase, to investigate the first double adaptive tau-amyloid-beta treatment, which involved combining lecanemab and the anti-tau antibody E2814 from Eisai [21]. As part of a novel prevention clinical trial called DIANTU, people with a family history of AD because of a specific 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. This type of genetic variation is responsible for about 1% to 5% of all cases of Alzheimer's disease [22]. Lecanemab was compared to a placebo in a phase III randomized, placebo-controlled, double-blind experiment to determine how well it affected cognition in early Alzheimer's disease. Lecanemab, among these mabs, shows promising results in the treatment of AD. It works by reducing the accumulation of amyloid-beta in the brain, which is a hallmark of the disease. This reduction in amyloid beta has been associated with an improvement in cognitive decline; additionally, the incidence of a side effect known as ARIA has been relatively low. Administered by intravenous infusion once every two weeks at a dosage of 10 mg/kg, lecanemab is safe and has a mild therapeutic effect in the studies. Further investigation is necessary to establish both the efficacy and safety of lecanemab[11].

2.1 Mechanism of action

Lecanemab is classified as an IgG1 monoclonal antibody, which functions by selectively attaching to both the soluble and insoluble forms of beta-amyloid proteins, which are the primary constituents of neurotic plaques that accumulate in the brains of individuals with AD. By binding to beta-amyloid, lecanemab is thought to help reduce the formation and accumulation of amyloid plaques, which may slow down the progression of AD. Lecanemab has also been shown to induce phagocytosis, or the process by which immune cells engulf and remove debris from amyloid beta aggregates, leading to their clearance from the brain. This mechanism is thought to be particularly important in reducing the level of toxic beta-

amyloid oligomers, which are believed to be the main drivers of AD pathology. Overall, the lecanemab mechanism of action involves binding to and facilitating the clearance of beta-amyloid aggregates from the brain, which mainly helps reduce the neurodegenerative effects of Alzheimer's disease[12].

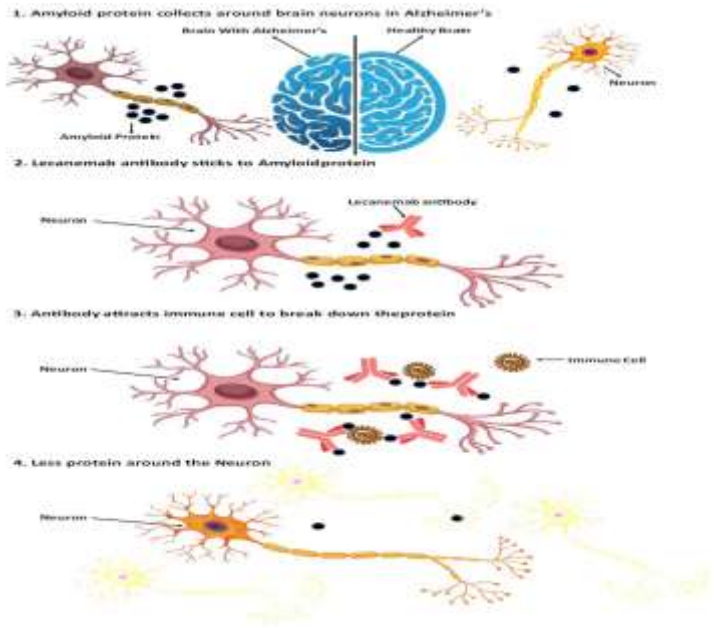

Figure 1: MECHANISM OF ACTION (LECANEMAB DRUG)

2.2 Clinical trials

Lecanemab is an experimental drug that targets beta–amyloid, a protein that accumulates in the brains of people with AD. Several clinical trials have been conducted to evaluate the safety and efficacy of lecanemab [23]. Lecanemab is being evaluated for safety and tolerability in phase one trials involving individuals with mild to moderate AD. 80 participants were enrolled [24,15]. The administration dosage for each dose of lecanemab during phase one trials varied between 0.1 mg/kg and 10 mg/kg given twice weekly[25]. In this study, the researcher evaluated the effect of a treatment on certain biological markers by analyzing samples of cerebrospinal fluid (CSF), conducting magnetic resonance imaging (MRI) scans, and monitoring for abnormalities related to amyloid imaging (ARIA), such as edema and haemorrhage[24]. The result of the experiment indicated that the incidence of ARIA-E/H in the lecanemab group was similar to that of the placebo group, and the half-life of lecanemab had approximately no impact on the CSF biomarker [24]. The primary drawback of these clinical trials was the inability to determine the optimal dosage for the treatment due to the lack of observable changes in the cerebrospinal fluid biomarkers [24] shown in Table 1. Subsequently, the focus of the study shifted to the effectiveness of lecanemab in a phase-2 trial with particular discoveries [19]. Following the completion of the phase one trial, the researchers devised phase two proof-of-concept trials utilizing a Bayesian methodology [25]. The goal of this experiment was to determine the BAN2401 dosage that would be most effective in treating early-stage AD patients at 90% effect [25]. The dosages of 2.5 mg/kg, 5 mg/kg, 10 mg/kg, and 10 mg/kg were used for two weeks, while 5 mg/kg and 10 mg/kg were used monthly, in line with the results of phase one trial [25]. For 800 subjects, a simulation of the study was used [21]. In the clinical trials of phase 2b stages, the investigators propose that decreasing amyloid plaques may be a viable approach to treating AD in its initial stages [26]. The number of participants in this study was 854 [12]. Despite not reaching its 12-month aim, this trial at

a dose of 10 mg/kg exhibited 64% superiority over the sugar pill group, instead of the intended 80% improvement [26]. The researchers also assessed the tolerability of lecanemab, and their findings showed a 9.9% incidence of amyloid–related imaging abnormalities, which include edema and hemorrhage (ARIA-E/H) [26]. At the 18-month mark, the overall tests demonstrated a decrease in amyloid–beta levels and a decrease in clinical decline, as evidenced by several endpoints [26] shown in Table 2. The most notable of these is the phase 3 clarity AD study, which enrolled 1795 patients with early AD[27]. In the Clarity AD study, patients were allocated randomly to receive either lecanemab or placebo. At 18 months, the study's primary endpoint was the alteration in the AD assessment scale cognitive subscale score compared to the baseline[28,29] shown in Table 3.

Table 1: Phase 1 Clinical Trials of Lecanemab[26-30].

Sponsor	Biogen
Study Design	Single–arm, open, Label, dose escalation
Date	Started in 2012 and completed in 2014
Number of Participants	80 individuals with mild to moderate AD
Duration	Four months
Result	Significant reduction of Aβ levels was observed in CSF in patients with AD receiving the highest dose of lecanemab

Table 2: Phase 2 clinical trials of Lecanemab[21-24]

Study Design	Randomized, double-blind, Placebo-controlled
Date	Complete in 2018
Number of Patients	854 people, of which 609 were treated with lecanemab & 245 were treated with placebo, with early-stage AD or mild cognitive impairment due to AD
Duration	18 Months
Primary Endpoint	Clinical dementia rating sum of boxes (Clinical Data Repository – small bowel) score variation between the baseline and 18-month periods.
Secondary	Changes in biomarkers of Alzheimer's disease, including amyloid

Endpoint	and tau levels, as measured by PET Imaging & (Cerebrospinal fluid) analysis
Result	The study's main goal was attained, with participants receiving lecanemab showing a significant decrease in Clinical Data Repository –small bowel score compared to placebo. The drug also knows radiation in Aβ plaques in the brain up to 93% but did not demonstrate significant cognitive benefits.

Table 3: Phase 3 clinical trials of Lecanemab[20-30]

Trail Name	Study 201 (Clarity AD)
Sponsor	Eisai Co. Ltd and Biogen Inc.
Date	Starting date – March 27 .2019, completion date- September 15, 2017
No. of participants	1795 individuals with early symptomatic AD, aged 50-90 years, from 331 sites in 15 countries.
Study design	A randomized, double-blind, placebo-controlled trial.
Treatment group	Lecanemab (10mg/kg) or placebo was administered intravenously to participants at random every four weeks for a total of 18 months.
Primary endpoint	At i8 months, the clinical dementia rating sum of boxes score showed changes from the baseline.
Secondary outcomes	Changes from baseline in AD assessment scale cognitive subscale (ADAS-Cog) score, brain amyloid levels measured by positron emission tomography (PET) imaging, and other measures of cognitive and functional decline
Result	In June 2021, Eisai and Biogen announced that the trial did not meet a statistically significant primary outcome reduction in CDR-SB score with lecanemab treatment compared to placebo. However, a pre-specified analysis of a subgroup of participants with mild AD did show a score Clinical Data Repository –small bowel drop that is statistically significant when lecanemab is used in place of a placebo.
Status	The trial is completed, but additional analyses are ongoing. Lecanemab is still under investigation for the treatment of AD.

Conclusion

The review paper gives an informative study about the new drug for Alzheimer's disease (Lecanemab), which can reduce Aβ plaques and prevent Aβ deposition in the brain. The various degrees of scientific evidence that support current AD therapy strategies reflect our knowledge of the disease's fundamental pathogenesis. Lowering tau and inflammation are two positive consequences that

follow the elimination of amyloid. The beta-amyloid pathway and amyloidogenic pathway recommend that a future remedy or prevention paradigm for AD strongly consider a precision medicine for the formation and deterioration of Aβ. A variety of attack angles are available for the numerous types of amyloid–beta, including soluble and insoluble monomers, oligomers, and plaques, giving doctors additional flexibility in developing a specific treatment plan to successfully slow AD progression in each patient. Lecanemab is one of the relatively safe passive immunotherapies that are at the forefront of developing novel treatments for AD. This research has also contributed to a growing body of evidence that shows passive immunotherapies are effective at preventing and treating neurodegeneration connected to Amyloid beta accumulation. Finding the majority of specialized Aβ vaccinations for a therapeutic protocol in the process of AD should be the main goal of future research. The lecanemab phase one trial did not produce encouraging findings since the optimal dosage could not be established. However, the phase II clinical trials demonstrated a decrease in Aβ and also lowered the deterioration in several therapeutic outcomes. Three phase three trials for lecanemab are currently being conducted. In addition, bidirectional research that examines the connection between mental or cognitive health and physical health may prove helpful in identifying the precise pathways by which this immunotherapy may likely improve AD.

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Conflict of Interest:

No Conflict of Interest

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