IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
June 2024 Vol.:30, Issue:6

Alzheimer's Disease and Special Focus on Lecanemab: Review of Literature

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ISSN 2349-7203
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Submitted: 23 May 2024
Accepted: 28 May 2024
Published: 30 June 2024

Keywords: Alzheimer's disease, β amyloid, Lecanemab, monoclonal antibodies, targeted treatment

ABSTRACT

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by progressive cognitive decline and eventually fatal dementia including memory loss, disorientation, impaired judgement and learning. AD ranges from asymptomatic to mild cognitive impairment. The accumulation of Amyloid β (Aβ) plaques and fibrillary tangles are the primary hypothesis which has been enlisted for the Alzheimer's disease. The CSF biomarkers consisting of these proteins can be detected via PET (Positron Emission Tomography) imaging. Lecanemab is a humanised IgG1 monoclonal antibody which potentially targets soluble Aβ. It also acts on insoluble fibrils. The FDA approved lecanemab, which effectively reduces Aβ plaque and addresses the underlying pathophysiology, has demonstrated superior clinical efficacy towards Aβ. As the research progresses, the manifestation of the molecular basis of the disease leads to the development of various possible targeted therapies.

INTRODUCTION:

Alzheimer's disease (AD) is the leading cause of dementia, characterised by progressive neurodegeneration (1). Dementia is more common in elderly people, with 5.3% of those aged 65-74 reporting the disease compared to over 35% of those aged 85 and above(2). The beta-amyloid (Aβ) plaques accumulate in the brain and assemble into soluble oligomers, causing acute neuronal damage and neurodegeneration(3). Significant progress has been achieved in developing therapy methods for Alzheimer's disease in recent decades(4). The FDA has approved these medications to treat Alzheimer's disease, that includes Acetylcholinesterase inhibitors, N-Methyl Receptor Antagonists (NMDA) and Monoclonal antibodies. Lecanemab, a humanised IgG1 monoclonal antibody, exhibits a high affinity towards soluble Aβ oligomers and protofibrils(4). The approval of these drugs serves as a hallmark in the therapeutic potential of Alzheimer's disease. More advancements are needed to increase efficacy, safety, convenience, and understanding of complex evidence like brain volume decline.(5)

ETIOLOGY:

The risks of the Alzheimer’s disease includes both genetic and environmental factors It increases with increase in age as the age factor plays a major role in the development of alzheimer’s. AD can be classified when the disease manifests, such as, early onset Alzheimer’s disease (EOAD) and late onset Alzheimer’s disease (LOAD) [table 1]. EOAD occurs before age 65 with mutations in the genes APP, PSEN1 or PSEN2 whereas LOAD occurs beyond age 65 where the causes are sporadic and irrelevant. But there’s no identifiable genetic cause for Alzheimer’s disease.(6)

TABLE 1: Risks leading to Alzheimer’s disease

GENETIC FACTORS	ENVIRONMENTAL FACTORS
• **PSEN 1** • **PSEN 2** • **APP**	• **Aging** • **Cardiovascular diseases** • **Metabolic syndromes** • **Severe traumatic brain injury**

EPIDEMIOLOGY:

Globally, the prevalence and the mortality rate that women have is 1.17 times greater than men. Alzheimer's disease became the sixth biggest cause of death in American elders, with a 146.2% increase in mortality rates between 2000 and 2018.(7)

PATHOPHYSIOLOGY:

The amyloid hypothesis was considered to be the dominant hypothesis in the research of AD. The genes responsible for the Aβ accumulation are PSEN1, PSEN2 and APP. Apart from these genes, abnormal accumulation of neurofibrillary tangles also results in AD(6). Therefore, the accumulated amyloid-beta (Aβ) proteins and tau proteins give rise to prime pathogenic events in the development and progression of AD. The imbalance of amyloid β in production and clearance is an initiating factor in the growth of the disease. Monoclonal antibodies (mAbs) are capable of inhibiting the pathologic amyloid β oligomers or plaque formation, which has been found to show considerable attention in slowing the progression of AD.(8)

APP:

The APP is processed through amyloidogenic or non-amyloidogenic pathway. the APP gets cleaved by the enzymes α, β and γ secretases and releases the peptide into the cytosol. These peptides accumulate and forms soluble oligomers, which in turn tends to form clusters near the synapse resulting in synaptic dysfunction and neuronal loss.(6), (9)

PRESENILINS:

The two genes Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2) encodes an enzyme complex involving APP processing which causes the mutation of autosomal dominant AD. It is also found to alter Aβ production, similar to APP processing, resulting in functional loss. Furthermore, PSEN1 accounts for majority of the cases in familial disease.(6)

TAU PROTEIN:

NFTs are intraneuronal neurofibrillary tangles of tau proteins. The tau protein plays a major role in the assembly and stability of microtubules. There are six isoforms of tau protein generated by the splicing of exon 10, which leads to the higher rate of the formation of 4R tau

ultimately leading to higher rate of degeneration and alteration in the transcriptional and axonal pathways. The tau will hyperphosphorylate prior to the NFTs formation, resulting in accumulation and potential toxicity of this protein. (6)

OTHERS:

AGE:

Age at onset (AAO) in AD families is strongly heritable. It is caused due to the mutations in the following three genes: Amyloid Precursor Protein (APP), Presenilin-1 (PSEN1), and Presenilin-2 (PSEN2). But, the genes involved in AAO variance are still largely unknown.(10)

CARDIOVASCULAR:

In AD, the brain becomes susceptible to cerebral perfusion impairment, which is a common cause for heart failure (HF), especially when it comes to reduced systolic function. The development of the genes involved in AD has been thought to be actively facilitated by cerebral hypoperfusion; however, there are currently insufficient data from human patients to support this theory. Acidosis and oxidative stress are the results of a metabolic energy crisis that cerebral hypoperfusion brings on in the brain cells. Tau proteins become hyperphosphorylated when lysosomal enzymes are stimulated to activate in an acidic environment. These tau proteins that have been hyperphosphorylated group together to form what are known as neurofibrillary tangles. (11)

METABOLIC:

First-line genetic factors are accountable for the onset of metabolic diseases and neurodegenerative disorders. The integration of nutritional signalling by cerebral regions, namely the hypothalamus, initiates a series of neurochemical reactions that establish the connection between brain functions and metabolism. Thus, the hypothalamic-pituitary-adrenal (HPA) axis alters the neurochemicals associated with metabolic syndrome. Insulin resistance is induced in the hippocampal region by glucocorticoids, and disruption of the HPA axis is linked to a number of pathological conditions, including as ageing, emotional disorders, and metabolic diseases, particularly type 2 diabetes. (12)

SEVERE HEAD TRAUMA:

Comparing pathological assessments of human TBI tissue with research using animal models, different conclusions have been reached. Both the injury's inherent heterogeneity and the tissue collecting techniques are probably to blame for this. However, a number of significant trends in the data have been identified. Among the most noteworthy findings is the correlation between TBI and AD pathogenic characteristics. For example, the acute response to brain injury has been shown to be accompanied by increased expression of the amyloid precursor protein (APP), which gives rise to the Aβ peptides that comprise senile plaques, by examining cortical regions from TBI patients with survival times ranging from 4h to several years.(13)

CLINICAL MANIFESTATIONS:

Recent memory loss, linguistic difficulties, mood swings, impaired judgement, and a gradual personality change are among the earliest symptoms. As the condition progresses, the individual's ability to learn and recall new knowledge declines. The behavioural difficulties of wandering, agitation, hostility, and bewilderment deepen, and the individual develops sphincteric incontinence and profound motor weakness, and becomes bedridden with entire dependence on providers for everyday duties (6). The characteristics and the manifestations are classified into multiple stages which is further discussed below in table 2.(6)

TABLE 2: The seven clinical stages of Alzheimer's disease (Global Deterioration Scale) (6)

STAGES	MANIFESTATIONS
STAGE I	When a person's cognitive appearance is normal, pathological brain changes are occurring
STAGE II	Prodromal stage: one experiences some memory loss, although it is usually not noticeable from ordinary forgetfulness.
STAGE III	In moderate cognitive impairment (MCI) progression, individuals could become disoriented or struggle to find the right words
STAGE IV	Mild dementia with impaired short-term memory. Some individuals lose track of their personal history.
STAGE V	As cognitive function continues to deteriorate, individuals now require care in their daily lives. They experience disorientation and often forget personal information.
STAGE VI	Extreme dementia. Needing ongoing attention and monitoring. Patients experience personality changes and lose the ability to identify many of their friends and family.
STAGE VII	People with AD need help eating, have motor incordination, struggle to communicate, and are incontinent.

DIAGNOSIS:

At present, the diagnosis of Alzheimer's disease majorly depends on the positron emission tomography (PET) imaging of the brain and the analysis of the cerebrospinal fluid (CSF) fluid. Phosphorylated tau protein gets secreted into the CSF which later crosses the BBB to enter the circulation, which can be used as a biomarker for AD. The diagnosis has an increased accuracy with PET where it used ligands for detection. But due to its exceeding cost it is not widely used. Therefore, biomarkers serve as a benchmark for the detection of AD. (14)

BIOMARKER:

A biomarker is an indicator used for evaluation of any normal biological as well as pathogenic processes and pharmacological effects of any therapy. In AD, hyperphosphorylated tau protein and deposition of the amyloid β (Aβ42) protein serves as the primary biomarker. (14)

CEREBROSPINAL FLUID:

The hydrophobic peptide, aggregates and becomes sequestered in plaques, with lower amounts remaining to be secreted to the extracellular space and the CSF, resulting in lower CSF levels of Aβ42. Tau protein can be detected quantitatively in CSF samples. The prime marker of AD in CSF shows the intensity of the severity. In the AD spectrum, higher CSF T-tau and P-tau predict a more rapid clinical disease progression supporting CSF T-tau as a biomarker for intensity of neuro degeneration. (45)

BRAIN IMAGING:

Amyloid and brain metabolisms are assessed with PET, whereas structural and functional imaging is done with magnetic resonance imaging (MRI). The most often employed imaging modalities are amyloid PET, fluoro-deoxy glucose (FDG), and structural and functional MRI. Diffusion tensor imaging (DTI) and related tractography technologies, arterial spin labelling measurements of cerebral blood flow, cholinergic system-targeted PET tracers, microglial activation, and other tracers are additional MRI techniques under development that are contributing to our understanding of AD. (14)

A functional MRI, can predict the regional blood flow. It has been shown that nondemented APOE-4 carriers exhibit higher levels of brain activity during memory tests than noncarriers, and the degree of activation is predictive of eventual cognitive deterioration.10. Magnetic resonance spectroscopy (MRI) and diffusion tensor imaging (DTI) can both measure the concentrations of metabolites or tissue substrate. (15)

GENETIC FACTORS:

A tiny percentage of instances of autosomal dominant AD shows unusual characteristics. The evidence has shown that autosomal dominant mutations are not associated with atypical AD traits. Patients who present with atypical phenotypes are less likely to carry the apolipoprotein E (APOE) ε4 allele. It is difficult to perform large-scale genetic studies with sufficient power due to the relative rarity of these presentations; nevertheless, a GWAS in PCA identified candidate genes implicated in processes related to intercellular communication and development in the visual and central nervous systems; these findings need to be confirmed and replicated. (16)

BLOOD AND URINE BIOMARKERS:

Aβ peptides secondary structure is a reliable blood biomarker for severe AD stages. The two major forms of amyloid β-peptides produced by the proteolytic cleavage of the amyloid precursor protein (APP) by β- and δ-secretases are Aβ40 and Aβ42. Aβ42 levels are linked to cognitive decline and rise as dementia progresses. A dominantly inherited form of early-onset AD caused by mutations in these genes are associated with elevated plasma Aβ42 and Aβ40 levels in patients prior to the onset of the disease. Additionally, the late-onset cases who are cognitively normal had higher amounts of both Aβ42 and Aβ40 in plasma. (14)

TREATMENT:

Reducing the levels of Aβ aggregation and plaques or increasing the brain clearance rate of Aβ is considered an effective therapeutic target for AD. The objective of treatment is to reduce behaviour issues associated with memory loss, psychosis, delirium, paranoia and improve cognition.(17)

GOALS OF THE THERAPY:

Treating cognitive impairments symptomatically and maintaining patient function for as long as possible are the main objectives of treatment for AD. Treating the behavioural and psychological aftereffects of the illness are secondary objectives. There is no evidence that the current treatments for AD can cure AD, extend life, or stop or reverse the pathophysiologic processes causing the condition. (35)

GENERAL TREATMENT APPROACH:

Early and ongoing cholinesterase inhibitor treatment has been shown to have modest advantages in clinical trials. The addition of memantine in cases of mild to severe illness may also be beneficial. Adhering to this strategy enables optimal improvement and preservation of cognitive function and day-to-day activities. When behavioural signs appear, they are treated symptomatically. (36)

Appropriate treatment requires educating the patient and family at the moment of diagnosis. This includes going over the duration of the illness, setting reasonable expectations for the course of treatment, and stressing the value of financial and legal planning. Effective communication is essential to preserving a therapeutic setting and reducing stress during the course of the illness (36).

PHARMACOLOGICAL INTERVENTIONS

The Alzheimer's disease is pharmacologically treated depending upon their symptoms which has been classified into Cognitive based and Non-Cognitive based.

COGNITIVE SYMPTOM BASED:

Cholinesterase inhibitors:

Numerous inhibitors of ChE have been created. There are now four medications on the market that are used to treat AD: galantamine, rivastigmine, and donepezil. Unfortunately, these medications have a restricted therapeutic window and have a variety of dose-related adverse effects, especially at larger dosages. Rivastigmine is a reversible inhibitor of both AChE and butyrylcholinesterase (BChE), whereas, galantamine and donepezil are AChE inhibitors. Compared to BChE, donepezil exhibits a notable high selectivity for AChE.(18)

NMDA receptor antagonists: Memantine

Memantine is an NMDA receptor (N-Methyl D-Aspartate Receptor) antagonist that can be used alone or together with cholinesterase inhibitors. It shows no benefit in mild Alzheimer's disease(19). Further elaboration is given in the table below:

TABLE 3: Treatment for Cognitive Symptoms (38) (39) (40) (41)

CHARACTERISTICS	DONEPEZIL	RIVASTIGMINE	GALANTAMINE	MEMANTINE
DOSE	Tablets: 5 mg, 10 mg and 23 mg Orally disintegrating tablets: 5 mg and 10 mg	1.5 mg, 3 mg, 4.5 mg, 6 mg	Tablet: 4mg 8mg 12mg Capsule:8mg 16mg 24mg Oral solution:4mg/mL	Tablet: 5mg, 10mg Oral solution: 2mg/ml
DOSAGE FORM	Tablets, orally disintegrating tablets	Capsule, oral solution, transdermal patches	Tablet, Capsule extended release, oral solution	Tablet, oral solution
MECHANISM OF ACTION	It is hypothesised that donepezil hydrochloride works via improving cholinergic function. This is achieved by reversibly inhibiting acetylcholinesterase's ability to hydrolyse it, therefore raising the concentration of acetylcholine.	Rivastigime reversibly inhibits cholinesterase enzyme to hydrolyse the acetylcholine resulting in its higher concentration.	Galantamine reversibly inhibits cholinesterase enzyme to hydrolyse the acetylcholine resulting in its higher concentration. As the disease progresses, the effects of galantamine might diminish.	Memantine acts an uncompetitive NMDA receptor antagonist thereby resulting in the inhibition of the excitatory NMDA receptor in CNS.
ADR	Nausea, diarrhoea, insomnia, vomiting, muscle cramps, fatigue, and anorexia	Nausea, vomiting, weight loss, anorexia	Nausea, Diarrhoea, Vomiting	Dizziness, headache, confusion constipation

NON-COGNITIVE SYMPTOM BASED:

Most AD patients experience noncognitive symptoms at some time during their condition. Three broad categories can be used to group these symptoms: symptoms of psychosis, unsuitable or agitated conduct, as well as depression. Behavioural symptoms are a major factor in the placement of patients in nursing homes since they are upsetting to both the patient and the carer, need more patience and oversight from the carer, and require effective management. In actuality, carer load is increased more by neuropsychiatric symptoms than by cognitive decline or neglect of oneself. (37)

TABLE 4: Treatment for Non- Cognitive Symptoms (42) (43) (44)

TABLE	**DOSE**	**TARGET SYMPTOMS**	**ADR**
ANTI-PSYCHOTICS Risperidone	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg	Psychosis, hallucinations, delusions, disruptive disorders	Somnolence, appetite increased, fatigue, rhinitis, upper respiratory tract infection, vomiting, coughing,
ANTI-DEPRESSANTS Citalopram	5mg, 10mg, 20mg, 5mg/ml (suspension)	Depression, anorexia, insomnia, anhedonia, suicidal	QT-Prolongation, Torsade de Pointes, Serotonin Syndrome
ANTI-CONVULSANTS Carbamazepine	100mg, 200mg, 400mg	Agitation, aggregation	Aplastic anemia, agranulocytosis, pancytopenia, Toxic epidermal necrosis (TEN)

IMMUNOTHERAPIES:

LECANEMAB:

Lecanemab (brand name: Leqembi), a humanised IgG1 antibody derived from mAb158, targets only soluble Aβ protofibrils . On January 6, 2023, the US FDA approved it via an accelerated approval pathway based on the findings of a phase 2 trial (NCT01767311) that demonstrated amyloid removal and the prospect of therapeutic effects.(20)

Aducanumab and Lecanemab targets soluble Aβ oligomers rather than plaques or fibrils, yet, Lecanemab revealed a tenfold increase in oligomer selectivity than aducanumab.(21)

TABLE 5: Key characteristics of Lecanemab (21)

CHARACTERISTICS	LECANEMAB
Type of antibody	IgG1 humanized N-Terminal
Amyloid species targeted	Large oligomers (protofibrils) > plaque
Dose	10mg/kg
Dose frequency	Once every two weeks
Route of administration	Intravenous
Serum half life	5.3 days
Penetration in brain	~ 0.5%
Most common effects	Microhaemorrhages, headaches, infusion related reactions

MECHANISM OF ACTION:

Lecanemab, a humanised monoclonal antibody, is found to exhibit higher affinity for soluble Aβ-protofibrils that are neurotoxic. This drug tends to decrease Aβ-fibril aggregation in astrocytes, reducing amyloid plaques and providing therapeutic advantages and disease modification. At 18 months, the deterioration in cognitive and functional assessments was moderately smaller compared to placebo. Aβ42/40 and p-tau181 are excellent plasma biomarkers for evaluating therapeutic effects of Lecanemab.(22)

PHARMACOKINETICS:

Lecanemab-irmb achieved steady-state concentration with the admininstration of 10mg/kg for every two weeks in a tsotal of six weeks period producing 1.4-fold systemic accumulation. It showed a dose-dependent rise in maximum concentration (Cmax) and area under the plasma concentration versus time curve (AUC). Lecanemab-irmb doses rose proportionally in the range of 0.3-15 mg/kg after a single dosage.(23)

PHARMACODYNAMICS:

Several clinical trials have examined the pharmacodynamics of Lecanemab. In phase II research (NCT01767311), at 12 and 18 months, Lecanemab showed significant lowered levels of Aβ than placebo. Clinically, improvement was dependent on dosage and time associated with lowered plasma levels of tau and Aβ. Thus, Lecanemab slows disease development and improves cognition, function, and everyday activities in patients.(3)

TRIALS:

PRECLINICAL:

In 2001, Nilsberth et al. (24)identified Aβ protofibrils as a pathogenic mechanism for Alzheimer's disease. A new APP mutation was discovered, that was found to accelerate the Aβ protofibril development and cause early onset symptoms. In a study using transgenic mice expressing the Arctic and Swedish APP mutations ('ArcSwe'), mAb158, initially developed to detect Aβ protofibrils, was found to diminish both soluble Aβ protofibrils and insoluble Aβ plaques when provided early in disease progression(25). A study of human post-mortem AD brains found that mAb158 binds to comparable soluble Aβ protofibrils (80-500 kDa) in human samples, resulting to the development of the humanised BAN2401. (26)

CLINICAL TRIALS:

PHASE 1:

The phase I clinical trial of lecanemab (NCT01230853) included 80 people and evaluated its safety, PK, and effects on plasma and CSF biomarkers [46]. The study included participants with mild to moderate Alzheimer's disease with an MMSE score of 16-28. Participants were randomly subjected to Single Ascending Dose (SAD) trial containing single doses ranging from 0.1, 0.3, 1, 3, 10, and 15mg, whereas in Multiple Ascending Dose (MAD) trial, the doses ranged from 0.3, 1, 3mg/kg which were administered once in 4 weeks, and 10, 15mg/kg were given twice in a week. Thus, the trials reported better toleration of Lecanemab at both the dosage levels. Based on the PK analysis report, Lecanemab has been shown to have a dose dependent response and a serum half-life of seven days with dosages ≥10 mg/kg. In SAD and MAD trials, Amyloid Related Imaging Abnormality- Microhaemorrhages (ARIA-H) was observed. (5)

PHASE 2:

A total of 854 randomised participants were treated (609 with Lecanemab and 245 with placebo). The ED90 10mg/kg that was administered twice a week had a 64% likelihood than placebo at 12months. Lecanemab, in comparison with a placebo, reduced the amyloid β plaques showing a significant difference in the treatment with a dose of 10mg/kg given twice a week, at 18 months. The prime biomarkers served to a provide a promising therapeutic

effect. Lecanemab was well tolerated, with a 9.9% incidence of amyloid-related imaging abnormalities (edema/effusion) at 10 mg/kg biweekly.(27)

Using data from the Phase II trial, the efficacy endpoints were developed from the longitudinal models of pharmacokinetics/pharmacodynamics for ADCOMS, CDR-SB and ADAS-Cog. Evidences from placebo-treated individuals were utilised to develop a disease progression model. The effect of Lecanemab exposure predicted by the model (maximum concentration at steady state [Css,max] and average concentration at steady state [Css,av]) on the development of the disease was investigated using data from each participant in the following ways:

$$\mathrm{EFF} - \mathrm{INT} + \mathrm{SLP} * (1 - \mathrm{DESLOPE} * (\text{Lecanemab Exposure})) * \mathrm{Time}$$

where EFF, INT, SLP, and DESLOPE stand for Lecanemab effect on disease progression rate (DES), baseline clinical score (INT), disease progression rate (SLP), and clinical scores of efficacy endpoints at each assessment time (EFF).(28)

PHASE 3:

For the individuals suffering from early Alzheimer's disease, an 18-month multicenter, double-blind, placebo-controlled, parallel-group trial was conducted, known as Clarity AD. Participants were randomly assigned to receive either intravenous Lecanemab (10 mg/kg every 2 weeks) or placebo.(29)

The primary efficacy criterion was the shift in the CDR-SB score between the baseline and 18-month marks which is a validated outcome measure for Alzheimer's disease. It assesses cognition and function through interviews with patients and carers(29). The primary outcome goal is to achieve Aβ plaque clearance on PET. Secondary outcomes include the change in Aβ plaque on PET from baseline, time to clearance, PK measure of trough serum concentration, and number of participants with treatment-emergent antidrug antibodies.(5)

The ADAS-cog14 score was -1.44 (95% CI, -2.27 to -0.61; P<0.001), the ADCOMS was -0.050 (95% CI, -0.074 to -0.027; P<0.001), and the ADCS-MCI-ADL score was 2.0 (95% CI, 1.2 to 2.8; P<0.001). Lecanemab caused infusion-related responses in 26.4% of participants and amyloid-related imaging abnormalities, including edoema or effusions in 12.6%.(29)

SAFETY:

In the CLARITY AD trial, 6.9% of the individuals taking part in the test, left due to the side events caused by lecanemab when compared to placebo. (31) Infusion responses were the most prevalent adverse event in the Lecanemab group (26.4% versus 7.4% for placebo). The majority of mild-to-moderate reactions occurred when the first dose was administered. The Lecanemab group had a higher rate of amyloid-related imaging abnormalities (ARIA), which is associated with this type of therapy (16). ARIA-H included cerebrovascular microhaemorrhages and superficial siderosis (Lecanemab: 17.3%; placebo: 9%) and ARIA-E effects included oedema or effusion (Lecanemab: 12.6%; placebo: 1.7%). The CLARITY AD trial revealed six deaths in the Lecanemab group and seven in the placebo group. Therefore, the investigators found no link between Lecanemab and ARIA-related mortality.(30)

Lecanemab's use during pregnancy has not been adequately investigated to determine whether it raises the chance of serious birth abnormalities, miscarriages, or other detrimental effects on the mother or foetus.(31)

EFFICACY:

At 18 months, the primary end point of the CLARITY AD study revealed adjusted mean changes in the CDR-SB with a score of 1.21 in the Lecanemab group and 1.66 in the placebo group. This indicates a significant statistical difference of -0.45 (95% confidence interval [CI], -0.67 to -0.23; $P<0.001$) in favour of Lecanemab. Therefore, the results showed that the Lecanemab group outperformed the placebo group significantly.(21)

SIDE EFFECTS:

Amyloid-related imaging abnormalities (ARIA) are related to cerebral micro haemorrhages, superficial siderosis, and brain parenchymal edoema. ARIA is often associated with anti-Aβ antibodies, which tend to increase its synthesis. ARIA was found to be more common in patients with greater medication dosages and ApoE4 alleles. (3) ApoE4 bearers have a higher risk of cognitive impairment, which is problematic given that genetic testing is typically not performed prior to treatment. Lecanemab may aggravate clinical symptoms in ApoE4 carriers with Alzheimer's disease. (3)

Monoclonal antibodies have distinct adverse effects compared to other Alzheimer's medications such cholinesterase inhibitors (donepezil, galantamine, and rivastigmine). The Phase III trial found no new safety concerns with Lecanemab, indicating a favourable safety profile overall. The results indicate that Lecanemab has a manageable safety profile and that its benefits outweigh the risks.(3)

CONTRAINDICATIONS:

LEQEMBI is not recommended for patients who experience or have a history of severe hypersensitivity to Lecanemab-irmb or any of its excipients. Angioedema and anaphylaxis were among the reactions. (23)

LEQEMBI has been linked to hypersensitivity events such as angioedema, bronchospasm, and anaphylaxis in patients. If signs or symptoms of a hypersensitive reaction is seen, discontinue the infusion immediately and seek medical treatment. (23)

COST AFFORDABILITY:

Lecanemab is an antibody that targets protofibrils, an intermediate phase in the production of amyloid plaques, to reduce their load in the brain. The FDA awarded Lecanemab expedited approval in January 2023 when the phase 2 trial exhibited a significant PET imaging of decreased amyloid protein. (32)

Lecanemab is infused intravenously every 14 days in expert health centres. Regular clinical follow-ups and magnetic resonance imaging (MRI) may be required.(32)

In the current study, the possible expenses of the first three years of mass prescribing Lecanemab was investigated with MCI per1,000,000 individuals in several situations. We investigated the status quo, a prophylactic scenario, and multiple imaging-assisted prognostication scenarios using different combinations of neuroimaging modalities with varying levels of sensitivity and specificity, and then compared the costs of pharmaceutical intervention under various pricing scenarios(33). The table below depicts the analysis of outcomes and the costs of both healthcare (highlight on direct medical care expenses and outcomes on patient health) and societal sector (emphasis of impact on patient productivity, caregiver’s time, quality of life and medical expenses) outlooks. The evaluated endpoints include QALY, evLY, life outside longterm care and life costs.(34)

TABLE 6: Model Outcomes for the Health Care Sector and Modified Societal Perspective

TREATMENT	INTERVENTION COST	TOTAL COST	LIFE YEARS	QALY	evLY	YEARS IN THE COMMUNUTY
HEALTH CARE SECTOR PERSPECTIVE						
Lecanemab	109000	489000	6.23	3.84	3.96	4.20
Supportive care	0	363000	5.77	3.34	3.34	3.69
MODIFIED SOCIETAL PERSPECTIVE						
Lecanemab	109000	790000	6.23	3.49	3.64	4.20
Supportive care	0	670000	5.77	2.98	2.98	3.69

All costs are presented in US dollars.

QALY- Quality Adjusted Life Year

evLY- Equal Value Life Year

CONCLUSION:

Alzheimer's disease being one of the most leading cause of dementia, is a irreversible, neurodegenerative disease affecting the age above 65. Both genetic and environmental factors result in amyloid β accumulation and abnormal tau proteins in the brain. These abnormal accumulation helps in the detection of the disease and to aim targeted therapy. Lecanemab, being the most successful monoclonal antibody, is effective against the reduction of soluble protofibrils and oliogomers. Despite having a reduced affinity for monomers, lecanemab binds to the small protofibrils 100 times and to the large protofibrils 25 times stronger stronger than other monoclonal antibodies. To lessen the risk of ARIA, people who have had more than four microhaemorrhages or who have cerebrovascular symptoms should be excluded. Lecanemab must not be given to the patients who are in need of anticoagulant or

thrombolytic therapy for strokes. Although, lecanemab shows promising results, further evidences are required to achieve better therapeutic targets.

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