BIOSPECIA
Content Available at www.uniquepubinternational.com/journals
(An International online peer reviewed Journal) ISSN (O): XXXX-XXXX
Review Article
OPEN ACCESS

Monoclonal Antibody Therapy in Early Alzheimer's disease: a Review of Lecanemab and Aducanumab

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Article History: Received: 14 Jan 2025, Revised: 27 Jan 2025, Accepted: 19 Feb 2025

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Abstract

Alzheimer's disease (AD) is a tragic and progressive neurodegenerative condition that impinges on the quality of life of the patient and impacting millions of people globally. Lecanemab (Leqembi) and Aducanumab (Aduhelm) are monoclonal antibody therapies for early Alzheimer's disease that bind and clear beta-amyloid plaques from the brain. Lecanemab targets β-amyloid protofibrils, has demonstrated encouraging efficacy in Phase III clinical trials for the therapy of early Alzheimer's disease (AD). Lecanemab has been approved by the FDA and has demonstrated significant efficacy in lowering Aβ plaque, thus treating the pathology. The therapy is given every two weeks via IV, taking approximately one hour to perform for each infusion. Magnetic resonance imaging (MRI) scans prior to initiation of treatment with lecanemab. Individuals have a genetic risk factor (ApoE ε4 gene carriers) that can result in an increased risk for the side effect of amyloid- related imaging abnormalities (ARIA). Lecanemab and Aducanumab can lead to amyloid-related imaging abnormalities (ARIA). ARIA is usually asymptomatic, but life-threatening and dangerous events are uncommon. ARIA leads to transient cerebral swelling that can be resolved with time and can be associated with bleeding in minor regions of the brain, but some individuals might present with symptoms like headache, confusion, dizziness, and changes in vision, nausea, and seizure. Aducanumab targets aggregated forms (plaque) of amyloid beta (Aβ) found in the brains of people with Alzheimer's disease to reduce its buildup. USFDA approved aducanumab onJuly, 2021, under accelerated approval, the first and sole treatment that addresses a major pathology of AD through the reduction of Aβ plaques in the brain.

Keywords: *Alzheimer's disease, Lecanemab, Aducanumab, Anti-Amyloid monoclonal antibodies, β-amyloid protofibrils.*

INTRODUCTION

The common cause of dementia is Alzheimer's disease. It is the biological process where the accumulation of proteins (amyloid plaques and neurofibrillary tangles) in the brain takes place. This leads to brain cells' gradual death and shrinkage of the brain [1].

Lecanemab is a drug that is approved to treat early-stage Alzheimer's disease. It is a monoclonal antibody designed to target and lower amyloid-beta plaques, which are thought to help cause the worsening of the disease. Although it has met with some success in halting the progression of cognitive impairment, it also poses a risk for severe side effects such as amyloid-related imaging abnormalities (ARIA), including swelling and bleeding of the brain [2]. Aducanumab was the first drug designed to directly target and remove the pathological protein deposits (amyloid-beta plaques) associated with Alzheimer's disease. It is a human immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to amyloid beta aggregates, promoting their clearance from the brain.In July 2021, the FDA granted accelerated approval for aducanumab; the decision was not based on the clinical data but rather on an intermediate outcome [3],

Table 1: Characteristics of Lecanemab and Aducanumab

Feature	Lecanemab	Aducanumab
Primary Target	Amyloid beta protofibrils	Aggregated amyloid beta (soluble and insoluble) fibrils
Binding Affinity	10 fold greater binding to protofibrils over fibrils	Binds to fibrils over protofibrils
Effect on plaques	Reduces amyloid plaques but with less affinity than	Targets in removing amyloid plaques

	protofibrils	

ALZEIHMERS DISEASE

Alzheimer's disease (AD) is defined as the presence of amyloid plaques and neurofibrillary tangles in the brain. The pathological changes predominantly involve the hippocampus and entorhinal cortex before extending to the rest of the brain, including the fronto- temporal cortices. The disease also comes with neurochemical deficits in the form of disturbances of neurotransmitter such as in the cholinergic system. The initial phases of AD are not easy to diagnose. A definite diagnosis can be established once cognitive impairment makes daily living activities difficult, even though the individual continues to live independently. The symptoms will evolve from mild cognitive difficulties, including memory loss through escalating phases of cognitive and non-cognitive impairments, cutting off all chances of independent existence, particularly during the latter phases of AD [4-6].

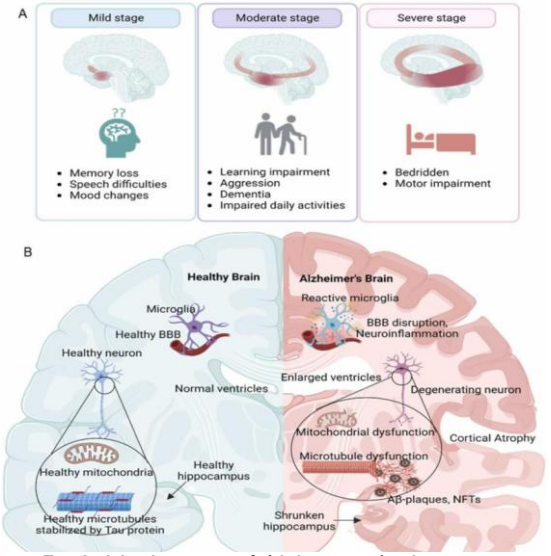

Fig 1: Mechanism of Alzheimer 's disease

Particular drugs that can lower the risk or development of Alzheimer's disease are those that target Aβ plaques, inflammation, APOE, neurotransmitter receptors, neurogenesis, growth factors or hormones [7].

PATHOPHYSIOLOGY OF ALZHEIMER'S

The Amyloidogenic pathway, APP is cleaved by β-secretase and γ-secretase to yield Aβwhich becomes aggregated. Aβ, 42, and 43 are greatly aggregated with Aβ. Therefore, the generated β-amyloid plaque can enhance oxidative stress and inflammation, which in turn change the kinase and phosphatase activity. This abnormally phosphorylates the tau protein, which is the primary reason behind the generation of NFT. Hence β-amyloid plaque and NFT lead to neuronal loss which ultimately results in AD [8-9].

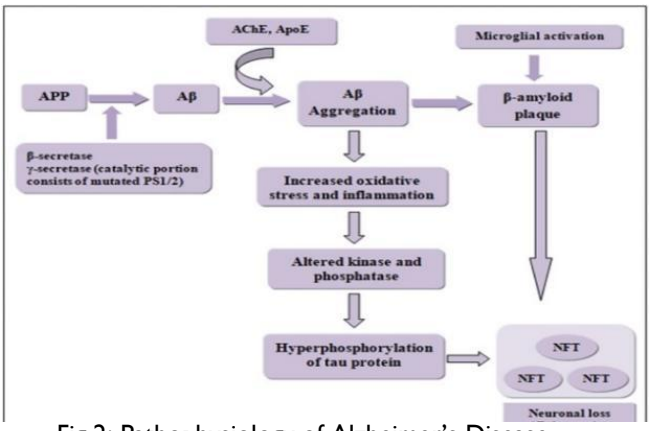

Fig 2: Pathophysiology of Alzheimer's Disease

MECHANISM OF ACTION

Lecanemab is an immunized monoclonal antibody that functions by binding to and clearing pathogenic forms of amyloid-beta (Aβ) protein, namely soluble Aβ protofibrils and amyloid plaques, from the brain. It is an immunotherapeutic strategy that seeks to halt disease progression, rather than reverse it. Aducanumab being an anti-Aβ monoclonal antibody lowers the plaque deposition by directly acting on both the aggregated insoluble and soluble Aβ. It binds to Aβ oligomers (ABO) and amyloid plaques in the brain at even low concentrations, initiating microglia activation for the degradation of amyloid species [10-12].

Side effects:

More common

Back pain, Blurred or changes in vision, Chest tightness, Chills ,Confusion, Diarrhoea, Dizziness, Drowsiness, Shakiness, Fever, Redness, General discomfort or illness, Headache, Pain in joints, loss of appetite, Aching and Pain in muscles, Nausea and vomiting, Nervousness, Paleness, Pounding in the ears, Runny nose, Seizures, Shivering ,Rapid or slow Heartbeat, sore throat, sweating, Difficulty breathing, Difficulty Sleeping, Unusual fatigue or Weakness [13].

Less common

Cough, Painful urination

Adverse Effects:

Lecanemab-

Infusion-related reactions, ARIA-H, Headache, ARIA-E, Cough, Diarrhea, Superficial siderosis of CNS, Rash, Nausea/vomiting, Lymphopenia, Atrial fibrillation, Intracerebral Hemorrhage

Aducanumab

Amyloid-related imaging abnormalities-edema (ARIA-E), Headache, ARIA-H microhemorrhage, ARIA-H superficial siderosis, Falls, Diarrhea, Confusion/ delirium/altered mental status/disorientation

Dose

Lecanemab is given by a healthcare professional through an intravenous (IV) infusion, where a needle is placed in a vein in your arm. It is administered every 2 weeks for the first 18 months, and then this can be prolonged to every 4 weeks. Each infusion will take

around 1 hour. The dosage of lecanemab recommended is 10 mg/kg. It is titrated and then given as an intravenous infusion over one hour, every two weeks for the first 18 months, and then this can be prolonged to every 4 weeks [14-16].

Available doses

Lecanemab 200 mg/2 mL (100 mg/mL) in a single-dose vial. The maintenance dose **of aducanumab** following a titration period (six doses) should be 10 mg/kg (administered by approximately one hour by intravenous infusion), with a gap of every four weeks, at least 21 days.

Prior to the treatment and prior to the 7th and 12th infusion (the first and sixth doses of 10 mg/kg respectively), the brain MRI is to be done.

Aducanumab can be supplied as 170 mg/1.7mL (100 mg/mL) or 300 mg/3mL (100 mg/mL) in a single-dose vial. Based on the results of the landmark trials and the phase 1b trial of aducanumab, the target dose is 10 mg/kg [17-19].

- 170 mg/1.7 mL (100 mg/mL)
- 300 mg/3 mL (100 mg/mL)

The dosage must be titrated, reaching 10 mg/kg at the seventh infusion. The IV infusion must be administered every 4 weeks with at least 21 days between infusions. The infusion must be administered during a 1-hour period [20].

Dosing Schedule

Treatment with aducanumab is titrated over time based on the following titration schedule:

- First infusion (1 mg/kg)
- Second infusion (1 mg/kg)
- Third infusion (3 mg/kg)
- Fourth infusion (3 mg/kg)
- Fifth infusion (6 mg/kg)
- Sixth infusion (6 mg/kg)
- Seventh infusion and beyond (10 mg/kg).

Table 2: Profile of Lecanemab and Aducanumab [3, 15]

	Lecanemab	**Aducanumab**
Brand Names	Leqembi	Aduhelm
Category	Anti-Beta amyloid monoclonal antibody	Anti-Beta amyloid monoclonal antibody
Dose	10mg/kg	Maintenance Dose-10mg/kg given with an interval of 21 days
Route of administration	Intravenous Infusion	Intravenous Infusion
Mechanism of Action	Targets soluble aggregated forms of amyloid known as protofibrils	Binds to aggregated forms of amyloid beta, including both soluble and insoluble fibrils with amyloid plaques
Effectiveness	It binds to small protofibrils with 100-fold the affinity of aducanumab and big protofibrils with 25 folds the affinity, with reduced binding affinity for monomers	lecanemab
Side Effects	Back pain, Chills, Confusion, Fever, Headache	Headache, Dizziness, Confusion, Vomiting
Adverse Effects	Infusion related reactions, ARIA-H, Headache, ARIA-E, Intra cerebral hemorrhage	ARIA-E,ARIA-H Micro-hemorrhage ARIA-H superficial siderosis, Falls
Contraindications	Serious Hypersensitivity reactions, Anti-coagulant therapy, Apolipoprotein E homozygosity	Anti coagulants, Parkinsonism, Stroke, ApoE4 ,Pregnant women
Interactions	42 major drug interactions are present-mainly with all anti-coagulants 3 moderate interactions	42 major drug interactions are present-mainly with all anti-coagulants 3 moderate interactions

Description	Lecanmab	Aducanumab
GENDER		
Males	490	227
Females	715	257
Unknown	112	29
AGE(yeatrs)		
Under 45 years	6	0
45-64 years	130	29
65-74 years	384	117
>75 years	503	168
Unknown	294	199

Table 3: Adverse Effects of Lecanemab and aducanumab

Adverse Effects	Lecanemab	Aducanumab
Headache	8.96%	3.74%
Fall	0.95%	2.05%
ARIAs	1.46%	1.51%
ARIA-edema/effusion	5.07%	13.79%
ARIA-microhemorrhages and hemosiderin deposits	4.5%	9.79%
Confusional State	2.96%	3.11%

Nausea	2.86%	0.71%
Dizziness	2.49%	1.51%
Chills	4.7%	0
Gait Disturbance	0.85%	0.98%
Infusion related reaction	3.95%	0
Pyrexia	2.9%	0
Vomiting	1.77%	0
Cerebral haemorrhage	0	2.49%
Tremor	1.74%	0
Asthenia	1.26%	0
Pain	1.23%	0
Diarrhoea	1.12%	0
Somnolence	0.99%	0
Feeling cold	0.89%	0
Superficial siderosis of CNS	0	2.05%
Seizure	0	1.78%
Brain edema	0	1.25%
Atrial Fibrillation	0	0.98%
Urinary tract infection	0	0.80%
Sub arachnoid haemorrhage	0	0.8%
Head injury	0	0.71%
Cerebro vascular accident	0	0.62%
Cerebral microhaemorrhage	0	0.62%

Table 4: Number of AEs reported for Lecanemab and Aducanumab from 2016-2024

Year of reporting	Lecanemab	Aducanumab
2016	0	18 (3.5%)
2018	0	1 (0.2%)
2019	0	2 (0.4%)
2021	0	18 (3.5%)
2022	0	226 (44.1%)
2023	1074 (81.5%)	200 (39 %)
2024	243 (18.5%)	48 (9.4%)
Total no.of AEs	1317	513

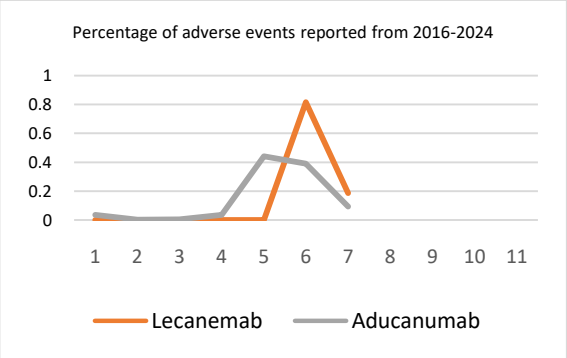

Fig 3: Percentage of adverse events from 2016 -2024

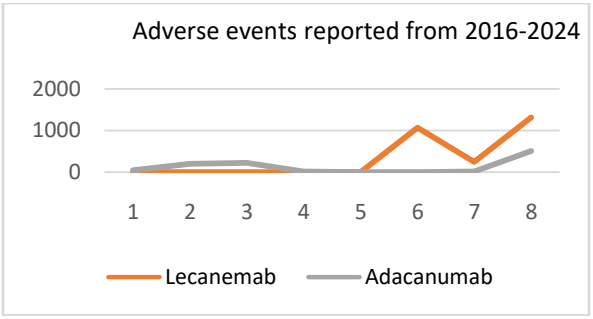

Fig 4: Adverse events reported from 2016-2024 from 2016-2024

Table 5: Number of AEs reported in different countries due to Lecanemab and Aducanumab

Country	Lecanemab	Aducanumab
Argentina	2 (0.2%)	0
Australia	2 (0.2%)	0
Canada	1 (0.1%)	5 (1%)
China	11 (0.8%)	0
France	4 (0.3%)	4 (0.8%)
Finland	0	3 (0.6%)
Germany	0	2 (0.4%)
Israel	1 (0.1%)	1 (0.2%)
Italy	3 (0.2%)	2 (0.4%)
Japan	69 (5.2%)	10 (1.9%)
Poland	0	1 (0.2 %)
Spain	2 (0.2%)	3 (0.6%)
South Korea	3 (0.2%)	0
Sweden	1 (0.1%)	1 (0.2%)
Switzerland	2 (0.2%)	4 (0.8%)
UK	3 (0.2%)	1 (0.2%)
US	1213 (92.1%)	475 (92.6 %)
UAE	0	1 (0.2%)
Total	1317	513

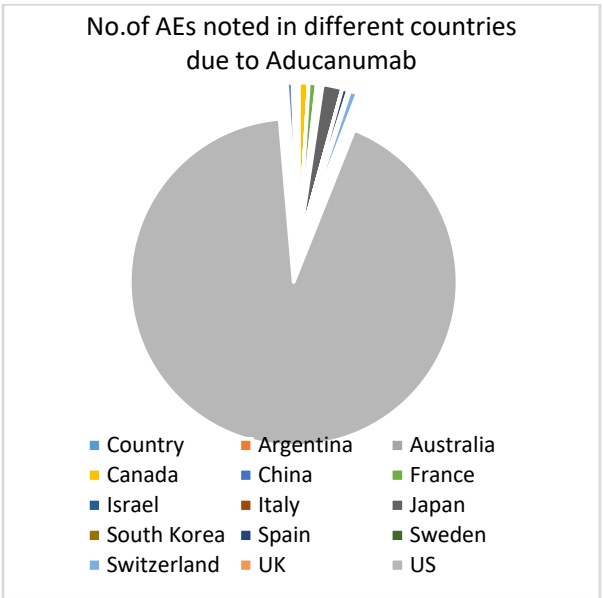

Fig:5-No.of AEs noted in different countries due to aducanumab

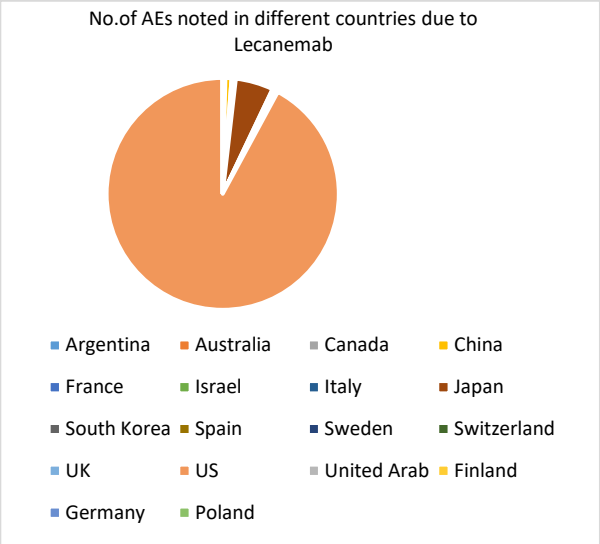

Fig 6: No.of AEs noted in different Countries due to due to lecanemab [21].

CONCLUSION

This study mainly focused on AEs of Alzheimer's Drugs (Lecanemab and Aducanumab).The brain related AEs are highly reported for Aducanumab as compared to Lecanemab (Brain Swelling, Micro haemorrhages, Cerebral Haemorrhages, Seizures, Confusional state, Siderosis of CN. etc,).Therefore Lecanemab is the more preferred treatment option for AD.

ABBREVIATIONS

AD-Alzheimer's Disease
NFT-Neurofibrillary Tangles
AEs- Adverse Events
ARIA-Amyloid related Imaging Abnormalities
ARIA-H- Amyloid related Imaging Abnormalities-Hemorrhage
ARIA-E- Amyloid related Imaging Abnormalities-Edema/Effusion
UK- United Kingdom
US-United States
UAE-United Arab Emirates

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