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A review on antibody of aducanumab- reduces the progression of Alzheimer disease

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Abstract
Alzheimer's disease which is the most common form of dementia and affecting millions of people, including family members who act as caretakers. This harmful disease is believed to account for 8% of total US healthcare spending, with health care workers costs amounting to approximately $29 billion. Alzheimer. The initial monoclonal antibody, to newly receive US FDA accelerated approval as moderate Alzheimer disease is aducanumab. Future therapies could be the first chemical approved to treat AD since 2003. The amyloid (A) pathway is becoming involved in the toxic of Alzheimer disease as it has evolved over time from a pathogen to a disease. - Biological structure. The approval of aducanumab is based on the reduction of the Amyload in the brain, which serves as a direct label for this signaling pathway. The fully human IgG1 monoclonal antibody aducanumab (BIIB-037) specifically binds to aggregated form A, inhibiting its matrix function and helping to clear plaque. There are three human trials that ended prematurely. Epidemiology, pathophysiology, and risk factors are discussed in this review, and presently aducanumab is the only drug approved for FDA that slows disease progression.

Keywords: AD - Alzheimer's disease, APOE - apolipoprotein, APP - amyloid precursor protein, Aβ - amyloid beta precursor, MCI - mild cognitive impairment

Introduction
Alzheimer disease is treated with the drug aducanumab. It is a monoclonal antibody directed against beta amyloid. This exercise consider the indications, functioning, and contraindications about aducanumab as a potential drug for the medicament of Alzheimer's disease. The progressive neurodegenerative disease known as Alzheimer's disease only affects people with mild dementia. This exercise presents the functions as the side effect profile, and other critical elements important to the multidisciplinary team treating patients with Alzheimer's disease (e.g, dose, pharmacodynamics, pharmacokinetics and monitoring, relevant interactions).Introduction

Alzheimer's disease
Alzheimer's disease is known as "dementia". Dementia is an umbrella word to a cognitive decrease severe enough to make it difficult to perform everyday action. Alzheimer's disease (AD) is the most form of dementia, accounting for at least two-thirds of dementia cases in people over 65 years of age. Alzheimer's disease is a neurological disorder that is the root of progressive decline in behavioral and cognitive skills such as storing, comprehension, speech, awareness's, reasoning and judgment. In the United States, Alzheimer's disease is the sixth major cause of death. Early outbreak (before age 65) is uncommon, occurring in less than 10% of patients with Alzheimer's disease. Alzheimer's disease has no cure, even if there are treatments that can relieve some indications. (Zilberzwige-Tal *et al*., 2018; Maccioni *et al*., 2018) [1, 2].
Alzheimer's disease (AD) is a growing neurodegenerative disorder most commonly indicate by early memory damage and cognitive decline that can eventually affect behavior, language, visuo-spatial orientation, and the motor system, and is the most common form of dementia. Variant ailment with early focal atrophy do not follow this traditional pattern, and pathologic of Alzheimer disease have been described. Clinical dementia in AD can only be definitively diagnosed after a post-mortem neuropathological examination, although research institutions able to assess amyloid and tau burden in patients challenge this historical pattern.

AD is also characterized by a long asymptomatic preclinical phase, and even people with normal cognitive function can have the disease. (Caselli *et al*., 2017; Johnson *et al*. 1999) [3, 4].

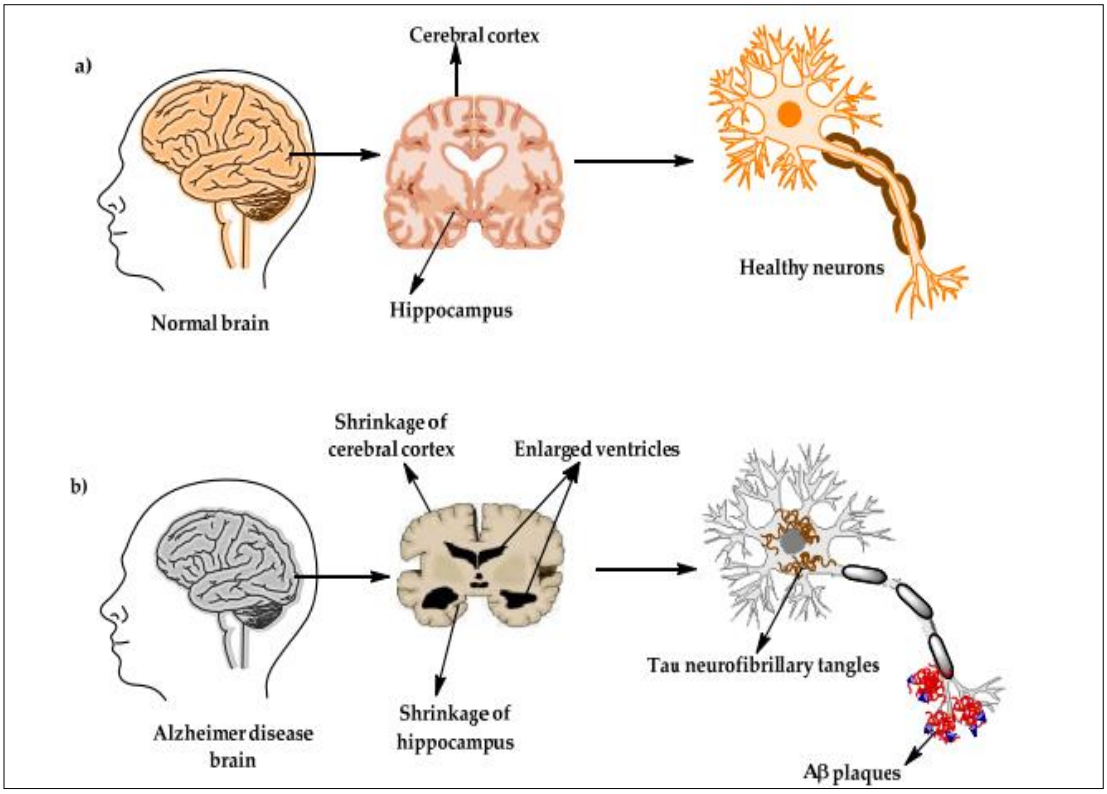

Fig 1: Physiological structure of brain and neurons in (a) Healthy brain and (b) Alzheimer disease brain

Alzheimer's disease is the form of dementia and can be defined as a slowly growing neurodegenerative disease. Alois Alzheimer, upon inspecting the brain of his first patient suffering from amnisia, noted the presence of amyloid plaques and massive neuronal loss and reported the disease as a severe cerebral cortical disease. Alzheimer's disease first appeared in its eighth version of the Textbook of Psychiatry. There is presently no cure for Alzheimer's disease, although treatments are available that only relieve the symptoms. On the basis of degree of cognitive impairment, Alzheimer's disease is divided into preclinical or presymptomatic, mild and dementia. These stages differ from the DSM-5 classification of Alzheimer's disease. The initial and most common symptoms are episodic short-term memory loss with relative sparing of long-term memory, and may be symptom-free in most patients. (Dhillon, S 2021) [5].

The genetic aspect of Alzheimer's disease appears to result from an autosomal control mutation in one of the presnilins on chromosome 21. Although the genetics of Alzheimer's disease are more complex and less well understood. The epsilon 4 allele of the apolipoprotein E (APOE) gene, located on chromosome 19, is known to be a risk factor for the development of sporadic Alzheimer's disease. Over the past two decades, advances in pathogenesis have prompted researchers to explore new drug therapies that focus more on the pathophysiological events of the disease. Extent of currently available treatments. Acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil) and an N-methyl-d-aspartate receptor antagonist (memantine) have minimal effect on disease progression and impair later stages.

Clinical dementia associated with Alzheimer's disease can be diagnosed after postmortem neuropathology, although research institutions able to assess amyloid and tau burden in living patients challenge this historical paradigm. The purpose of this review article is to provide a brief introduction to Alzheimer's disease, its pathology, cause and current treatment, and to highlight the recent modification of compounds that can prevent and treat Alzheimer's disease. Beta and tau aggregation and abnormal inflammatory folds. (Mahase, E 2021) [6].

Pathophysiology

Alzheimer's disease is characterized by the growth of abnormal neuritic plaques and neurofibrillary tangles in the brain. Plaques are small spherical lesions with an extracellular amyloid beta peptide core nearby enlarged axon terminals. Amyloid beta peptide consists of an amyloid precursor protein that is a transmembrane protein (APP). Proteases known alpha, beta, and gamma secretase degrade the amyloid beta peptide of APP. APP is often cleaved by alpha or-beta secretase and the small fragments produced are not dangerous to neurons. On the other hand, sequential cleavage by beta followed by gamma-secretase yields 42 amino acid peptides (beta-amyloid 42). An increase in amyloid-beta 42 leads to aggregation of the amyloid, leading to neurotoxicity. Amyloid beta protein 42 promotes the production of aggregated fibrous amyloid. (Verma *et al*., 2018) [7].

Neurofibrillary tangles are intracytoplasmic fiber aggregates generated in nerve cell by the protein tau. The main function of the tau protein is to stabilize axonal microtubules.

Microtubules are essential for intracellular transport, traversing the axons of neurons. The tau protein holds all microtubules together. Due to the growth of extracellular amyloid-beta, the tau protein is hyperphosphorylated in Alzheimer's disease, leading to the formation of tau aggregates. Tau aggregates produce neurofibrillary tangles, which are twisted, paired helical fibers. They start in the hippocampus and can spread to the cerebral cortex. Tau aggregates accumulate in neurons. Braak & Braak have developed a classification system found on the six-level topographical classification of neurofibrillary tangles, and this classification scheme by Braak is used. (Wallace *et al*., 2018; Song *et al*., 2014) [8, 9].

Symptoms of Alzheimer disease

- Memory loss
- Depression
- Mood swing
- Changed in sleeping habits

Stages of Alzheimer

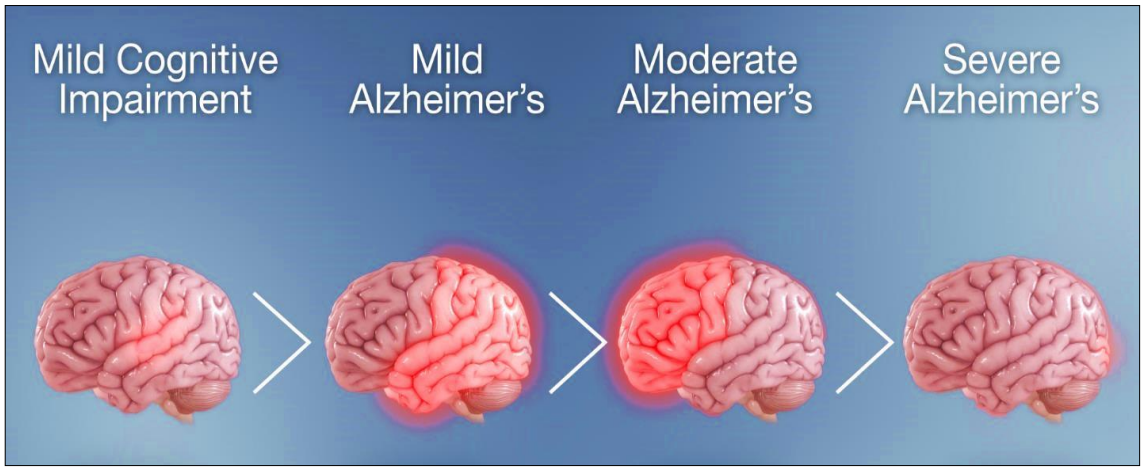

Fig 2: Stages of Alzheimer disease

- Preclinical Alzheimer disease (Dubois *et al*., 2016) [10].
- The mild cognitive impairment is caused by Alzheimer's disease (Kumar *et al*., 2020) [11].
- Mild dementia due to Alzheimer ailment (Kumar *et al*., 2020) [11].
- Severe dementia due to Alzheimer disease

Causes of Alzheimer disease

Alzheimer's disease is a multifactorial disorder the two most advanced hypotheses as the cause of Alzheimer's disease.

1) Cholinergic hypothesis
2) Amyloid hypothesis

1) Cholinergic hypothesis

In the 1970s, it was reported that cholinergic deficiency in the neocortex and presynaptic cortex is linked to the enzyme choline acetyltransferase, which is responsible for the synthesis of acetylcholine (Ach). Because of its important role in cognitive functions, the cholinergic hypothesis of Alzheimer's disease has been proposed. Ach is in the cytoplasm of cholinergic neurons from choline and acetyl-coenzyme A by the HAT enzyme and transported to the synaptic vesicle acetylcholine transporter (VACHT). In the brain, pain is involved in several physiological processes such as memory, attention, sensory information, learning, and other critical functions. Degeneration of cholinergic neurons has been shown to occur in Alzheimer's disease, leading to cognitive changes and memory loss. Amyloid-beta is thought to influence cholinergic neurotransmission and cause decreased choline uptake and release. Peptide. (H Ferreira-Vieira *et al*., 2016; Barbosa *et al*., 1997) [12, 13].

2) Amyloid Hypothesis

For a decade, anyway deposition of beta plaques in the central nervous system was found to be strongly correlated with dementia, leading to the conception of the amyloid hypothesis. However, it has also been found that amyloid plaques accumulate with age in normal, healthy brains. Alternative hypotheses for non-hereditary AD have been proposed in recent years, but currently the amyloid hypothesis remains the most accepted pathologic mechanism for hereditary AD. The amyloid hypothesis advice that the degradation of APP-derived Aβ by beta and gamma secretase decreases with age or disease, major aggregation of Aβ peptide (Aβ 40/Aβ 42). Increasing the dose of Aβ 42-A Aβ 40 increases the formation of Aβ amyloid fibrils leading to neurotoxicity and tau pathology leading to neuronal cell death and neurodegeneration. It has been found that Alzheimer's disease risk factor and mutation of several genes such as APP, PSEN1 and PSEN2 affect Aβ catabolism and anabolism, resulting in rapid accumulation of Aβ and rapid development of neurodegeneration. (Kametani *et al*., 2018) [14].

Risk factors

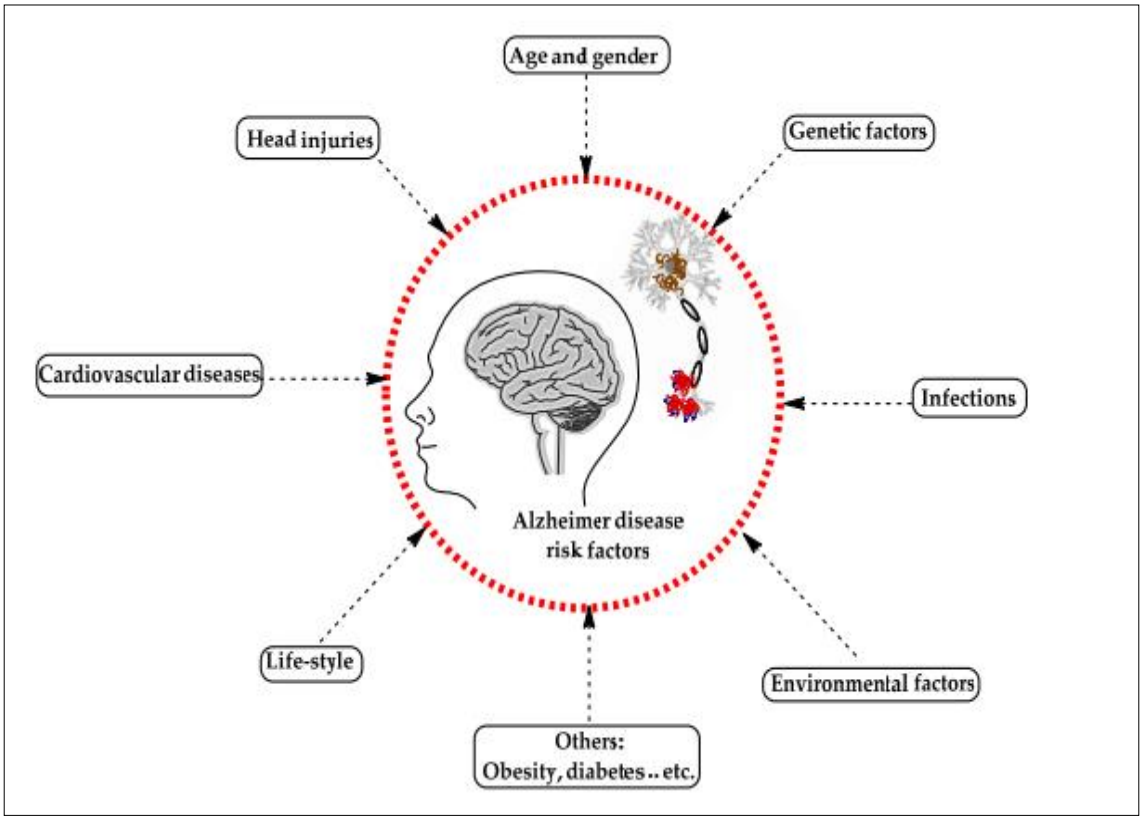

Fig 3: The risk factor for Alzheimer Disease

1) Aging

The most predominant risk factor for Alzheimer's disease is age. Young person rarely get the disease, and most Alzheimer's disease occurs late after the age of 65. (Guerreiro *et al*., 2015) [15]. Aging (Gueererio) Aging is a complex and irreversible process that occurs in many organs and cellular systems with a reduction in brain volume and mass and the loss of synaptic areas, accompanied by deposition of SP and NFT.In addition, various conditions that promote aging can occur, such as B. glucose deficiency, hypo metabolism, cholesterol dyshomeostasis, mitochondrial dysfunction, depression and cognitive decline. These changes also occur during the normal aging process, making it difficult to distinguish causes in the early stages of Alzheimer's disease. (Riedel *et al*., 2016; Hou *et al*., 2019; Fang *et al*., 2016) [16, 17, 18].

2) Genetics

Genetic factors have been found over the years and have been shown to play a main role in the development of Alzheimer's disease. 70% of Alzheimer's cases are linked to a genetic factor. (Van *et al*., 2016; Jaydev *et al*., 2010) [19, 20].

- Amyloid precursor protein
- Presenilin (PSEN1) (PSEN2)
- Apolipoprotein (APOE)
- Clusterin gene

3) Environmental factors

Environmental risk causes including:

- Air pollution
- Diet
- Metals
- Infection

4) Medical factors

a) Cardiovascular disease

Cardiovascular diseases are considered an important main factor for Alzheimer's disease, such as B. Stroke associated with an increased risk of dementia due to the loss of nerve tissue, which aggravates the degenerative effect and affects the pathology of amyloid and tau. (Santos *et al*., 2017) [21].

b) Obesity

Obesity is a term used to refer to a person's excess body fat resulting from consuming more calories than they burn and can be compute using body mass index. Increased body fat is related with decreased blood flow to the brain, promoting cerebral ischemia, memory loss, and vascular dementia. (Pegueroles *et al*., 2018) [22].

Treatment of Alzheimer Disease

Strategies currently available AchEIs and NMDA receptor antagonists. Novel strategies have been developed to modify the disease process. In this regard, important developments are moving towards Aβ- and tau-based drugs. This is the main key to deciphering this disease in the future. In this article, we have highlighted the currently approved treatment and some targeted therapeutic drugs.

Aducanumab

Aducanumab, a approved drug, is a monoclonal antibody that targets beta-amyloid. It is recommended for the medicament of Alzheimer's disease (AD). Moderate cognitive impairment or mild dementia with progressive neurodegenerative disease is the only case where the

indications for aducanumab in Alzheimer's disease are applicable to patients. First indication for initiating treatment with aducanumab, recommending treatment for all patients with Alzheimer's disease The disease progresses slowly, causing a gradual reduce in behavioral and cognitive abilities, first manifesting as impairment in short-term memory, followed by impairment in language, attention, comprehension, and executive functioning. Because there is no cure or effective treatment for Alzheimer's disease, current symptomatic treatment includes the use of cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) antagonists. (Sevigny *et al*., 2016) [23].

Aducanumab mechanism of action

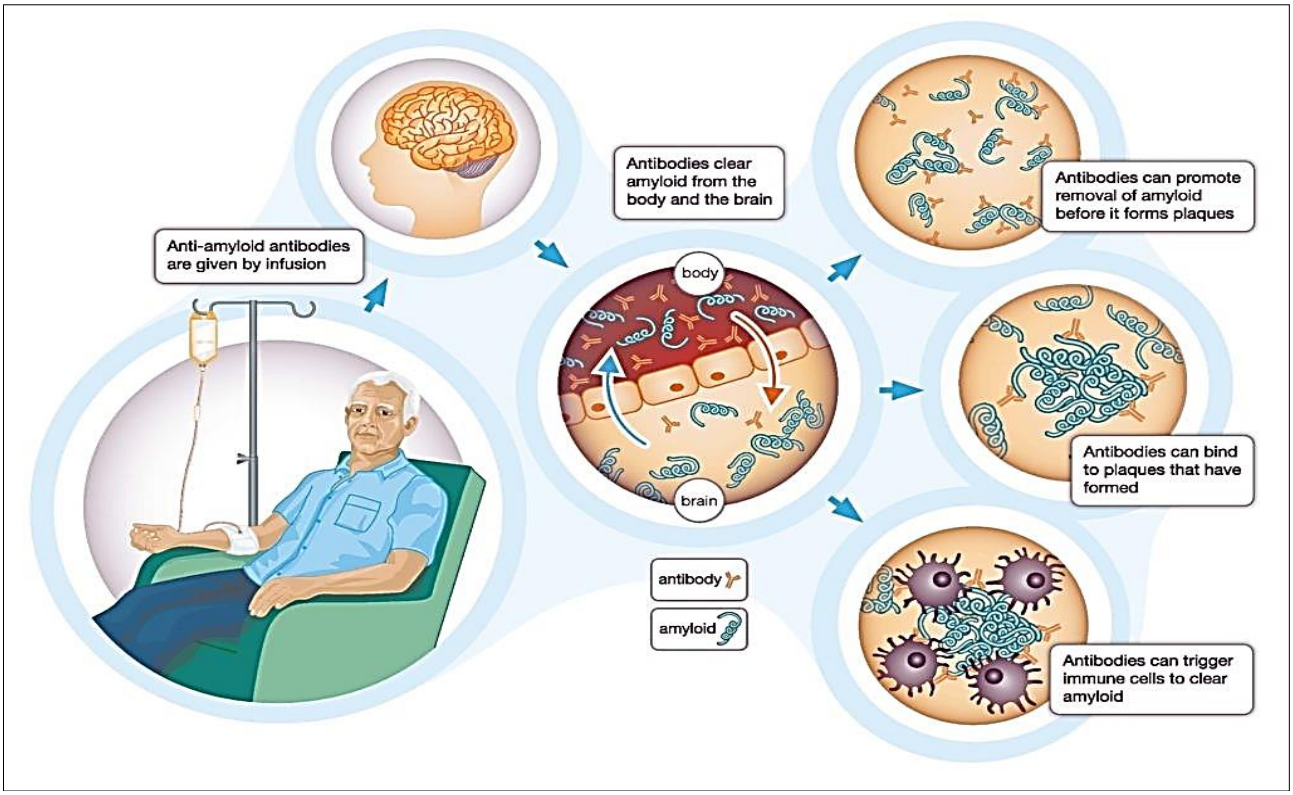

Fig 4: Mechanism of action: aducanumab

Aducanumab is an immunotherapy drug classified as a human monoclonal antibody immunoglobulin gamma1 (IgE1). It exerts its mechanism of action by crossing the blood-brain barrier and selectively targeting and binding to aggregated soluble oligomers and insoluble Aβ fibril conformations in the brain. (Sevigny *et al*., 2016; Kastanenka *et al*., 2016) [23, 24].

Biochemical and structural analyzes showed that aducanumab binds to a linear epitope formed from a linear epitope formed from Aβ amino acids 3 to 7. Compared to previously tested antibodies, aducanumab attach to the N-terminus of Aβ in an elongated conformation. Based on the low monovalent affinity, fast binding kinetics, and high avidity of epitope-rich aggregates, aducanumab has been appear to distinguish Aβ monomers from oligomeric or fibrillar aggregates. Increased selectivity of aducanumab for aggregated forms of Aβ leads to a reduction of Aβ plaques in the brain in a small subset using tau-PET. (Cumming *et al*., 2021) [25].

Aducanumab is a full-length, Aβ-selective human monoclonal antibody composed of a soluble oligomer and insoluble fibrils. Aducanumab treatment was evaluated in a clinical study in a subset of patients with mild cognitive impairment. The higher dose of aducanumab infusion caused a slight slowing of cognitive decline in patients with mild cognitive impairment. (Arndt *et al*., 2018) [26].

Table 1: Monoclonal Antibody

Monoclonal Antibody	
Type	Whole human body
Source	Human
Target	Amyloid Beta Protein

Table 2: Clinical data

Clinical data	
Trade names	Aduhelm
Other names	Aducanumab - avwa BIIB037 BIIB-037
Route	Intravenous

Aducanumab (Aducanumab - Avwa, Aduhelm) is a human monoclonal immunoglobulin gamma (IgG1) antibody managed against aggregated soluble and insoluble forms of amyloid B. It was jointly developed by Biogen and Eisai under license from neurimure for the treatment of Alzheimer's disease. In June 2021, aducanumab accept its first US approval for the treatment of Alzheimer's disease. Per U.S. FDA recommendations, in patients with wild-type or wild-type cognitive impairment with mild disease, treatment should be initiated in the treatment-initiated population in clinical trials. There are no data on the safety or efficacy of starting treatment earlier or later than in the study.

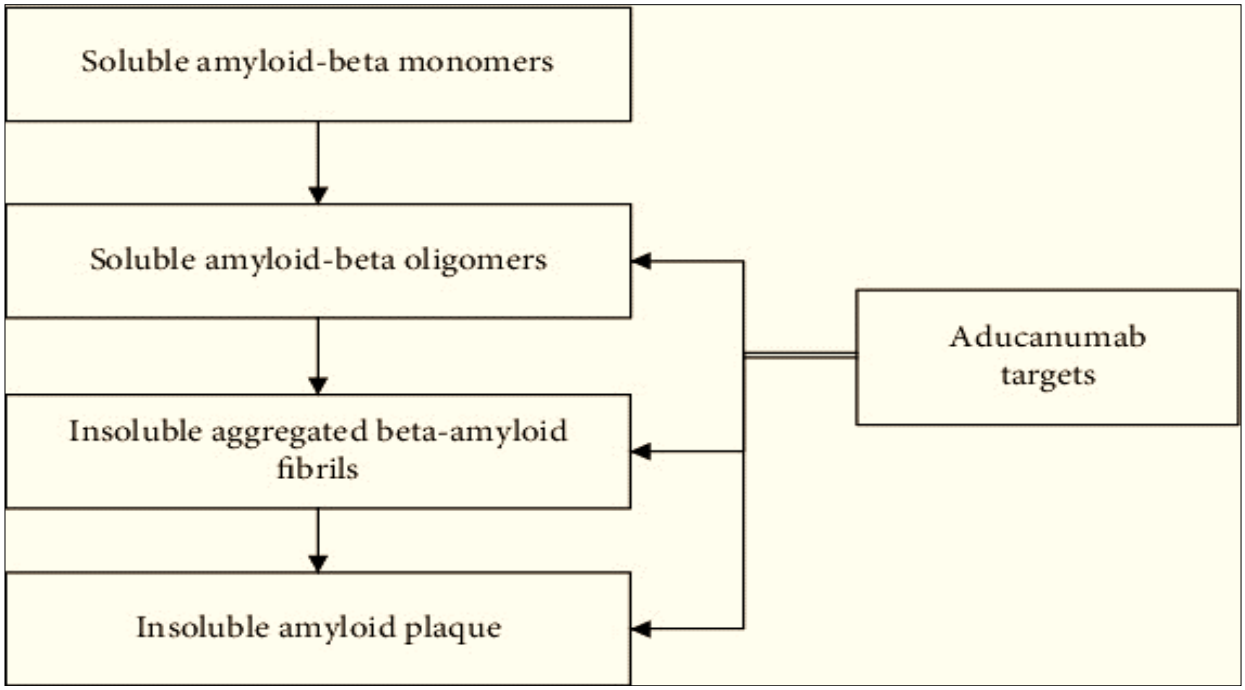

Fig 5: Mechanism of action: aducanumab

The two most well-known phase III trials for aducanumab are Engage and Emerge. The Emerge trial found that after 78 weeks of investigation, there was a 22% lower rate of cognitive deterioration in the group of participants receiving high-dose aducanumab compared to that of the placebo group in individuals with mild cognitive impairment (MCI) and mild dementia caused by AD. In the trial, the experimental group deteriorated quicker than the control group.

A dose-dependent reduction in amyloid deposition was seen in both groups using Positron Emission Tomography (PET) imaging. Following tests, aducanumab's biologics licensing application was sent to the Food and Drug Administration (FDA). In 2021, the medication received approval. The medication has a wide range of uses and is accepted by patients. (Conway, M. E, 2018) [27].

Aducanumab pharmacokinetic and Pharmodynamics

Aducanumab drastically reduces the production of Aβ oligomers by disrupting the kinetics of amyloid aggregation, a process involving primary nucleation from a monomeric protein and secondary nucleation onto managing fibrils. Pharmacodynamic studies with aducanumab have shown that the drug binds to and targets fibrils for microglia-mediated clearance, breaking the bridge connecting neuroprotective amyloid monomers and neurotoxic amyloid oligomers. Aducanumab can produce these effects, however, therapeutic amounts must be able to cross the blood-brain barrier and sustainably stimulate the destruction of amyloid aggregates.

Due to its long half-life, the drug reaches its maximum clinical welfare after approximately 5 months of use. Several other variables can affect latency, including time to clearance of amyloid plaques, individual amyloid burden, APOE ε4 genotype, age, and disease severity. This could explain why the high-dose group in the appear study resulted in the largest decreases in the rate of cognitive decline; relatively more patients in this group were able to achieve a sustained state of equilibrium in the brain. (Hardy *et al*., 1992) [28].

Storage condition for Aaducanumab

After dilution, it should be used immediately. If not used immediately, store the solution diluted in 0.9% sodium chloride solution. Store in a refrigerator at 20°C to 80°C for up to 3 days or at room temperature to 30°C for 12 hours.

Effectiveness of aducanumab

Aducanumab at a dose of 30 mg/kg was effective in treating Alzheimer's disease and was well tolerated with no potential side effects. Aducanumab is a new immunotherapy that may help reduce the pathological damage of Alzheimer's disease and reverse or slow cognitive decline. A study of the effectiveness of aducanumab was conducted, showing that it enters the brain and anti-beta amyloid levels decrease over time and in a dose-dependent manner. After approximately 15 months of treatment with aducanumab, data indicate that doses of 3 mg/kg, 6 mg/kg and 10 mg/kg result in a significant reduction in beta-amyloid plaques in patients with Alzheimer's disease. They also conducted a preclinical study in rats and administered a dose of 30 mg/kg intraperitoneally to counteract the fact that a dose of 30 mg/kg is required for diffusion and tight binding to beta-amyloid.

In this study, they found adverse drug reactions such as headache, urinary tract infection, and upper respiratory tract infection associated with abnormal amyloid-associated imaging (ARIA). In a phase I clinical trial, 166 patients having mild prophylaxis or mild symptoms were treated with aducanumab at doses of 1, 3, 6 or 10 mg/kg. Every 4 weeks and after 54 weeks of treatment, doses of 3 and 10 mg/kg of the drug significantly reduced brain Aβ levels and improved cognition, with the highest dose of being more pronounced than placebo. Although the results of the 6 mg/kg group did not differ from those of the 3 mg/kg and 10 mg/kg groups, the 6 mg/kg dose was able to increase Aβ

levels in the brain to decrease significantly, which slowed down the mental performance of the patient. Waste.

Aducanumab can be used in conjunction with ultrasound to not only improve perception but also reduce the burden of amyloid beta plaques. They found that an aducanumab analogue or ultrasound alone can reduce amyloid beta plaque burden, but the combination therapy has the additional effect of improving cognitive function, as confirmed by the Active Place Avoidance (APA) study. All other patients receiving aducanumab 60 mg/kg developed one systemic adverse event of pre-symptomatic amyloid imaging abnormalities (SARIs). They were also fully reversed in 2-3 months. Accumulations of amyloid proteins in the brain (plaques) are a neuropathological sign of Alzheimer's disease and are believed to trigger an issue of changes leading to cognitive decline.

Aducanumab is a monoclonal antibody that clears amyloid plaques. The study concluded that aducanumab's long-term efficacy, showing a positive outcome without significant side effects, makes this molecule a beacon of hope for patients. Some see aducanumab as evidence for the amyloid cascade theory, justifying decades of failed research that have cost billions of pounds and exposed thousands of participants to the side effects of experimental treatments. Another worries it simply encourages investment in anti-amyloid therapies and diverts attention from effective preventative measures like improving physical activity or lowering high blood pressure. (Synnott *et al*., 2021) [29].

Conclusion

Alzheimer's disease is an irreversible age-related neurodegenerative disease in which causes the death of nerve cells leads to memory loss, behavioral changes, loss of functioning, and cognitive impairment that impairs a person's ability to perform daily activities. The main reason of Alzheimer's disease is the accumulation of amyloid beta plaques and neurofibliary tangles in and around brain cells. Aducanumab is the first and only treatment that addresses the core pathology of Alzheimer's disease by reducing AB plaques in the brain. Aducanumab has the ability to slow the progression of Alzheimer's disease.

Discussion

In the current situation, we investigated whether aducanumab is effective in Alzheimer's disease. Alzheimer's disease is a neurodegenerative disease of the brain. Characterized by the accumulation of beta-amyloid protein plaques and neurofibrillary tangles, it is considered a neural and neural injury and results in loss of cognitive and physical function. Alzheimer's disease is the form of dementia, affecting millions of people, including family members who often act as caregivers. This devastating disease is said to consume 8% of the total in the United States. Health spending. With an estimated medical and nursing cost of US$290 billion, cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists have historically been the most commonly used drug treatments for AD patients, but these drugs are not curative.

This overview deals with epidemiology. Pathophysiology, risk factors and current treatment of AD Next, the role of the new monoclonal antibody aducanumab in the treatment of AD. -Currently, aducanumab is the only drug approved by the Food and Drug Administration to inhibit the progression of this disease. Symptoms of Alzheimer's disease include: Memory loss that interferes with daily living Poor judgment leading to poor decisions Loss of spontaneity and a sense of initiative Loss of orientation to data or current location Normal daily activities require more time to complete Repeated questions or forgetting recently known information.

It is a progressive disease beginning with mild memory loss and possibly leading to loss of the ability to carry on a conversation and respond to the environment. Alzheimer's disease involves parts of the brain that control thought, memory, and language.

The FDA recently approved aducanumab (Aduhelm) for people with mild symptoms of Alzheimer's disease, such as: B. for those who are still independent in daily life. It decreases amyloid plaques (protein buildup) in the brain, a hallmark of Alzheimer's disease. Binds specifically to aggregate forms of amyloid beta and recognizes amyloid plaques in brain tissue. When transgenic mice were treated systemically with aducanumab, the antibody was found to enter the brain and bind to amyloid-beta in the brain parenchyma. Aducanumab is a recombinant human monoclonal antibody G1 (IgG1) designed to promote clearance of brain amyloid deposits and insoluble forms of Aβ.Aducanumab drastically reduces the production of Aβ oligomers by disrupting the kinetics of amyloid aggregation, a multistep process involving primary nucleation from a monomeric protein and secondary nucleation on existing fibrils. Pharmacodynamic studies of aducanumab have resulted that the drug binds fibrils and targets them for microglial-mediated removal, interrupting the bridge between neuroprotective amyloid monomers and neurotoxic amyloid oligomers.

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