

(REVIEW ARTICLE)



## Drug information of Aducanumab and its effectiveness for Alzheimer's disease: A clinical review

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### Abstract

Alzheimer's disease (AD) is the main cause of disability in people older than 60 years. More than 1 million cases per year reported in India. AD and other kinds of dementia are more common as individuals become older, affecting 1 in every 14 people over the age of 65 and 1 in every 6 people over the age of 80. ADUHELM (Aducanumab) is a monoclonal antibody, new class of medication needed for treatment of AD. The latest drug used to treat underlying cause of AD and recent studies shown to be efficacious and safe for the AD. Our review emphasizes on the drug information of Aducanumab and its clinical importance in AD.

**Keywords:** Alzheimer's disease; Aducanumab; Drug information; Genetic mutations.

### 1. Introduction

Early onset Alzheimer disease (EOAD) is a neurodegenerative dementing disorder that is relatively rare (<1% of all Alzheimer cases). Various genetic mutations of the presenilin 1 (PSEN1) and presenilin 2 (PSEN2) as well as the amyloid precursor protein (APP) gene have been implicated. Mutations of PSEN1 and PSEN2 alter  $\gamma$ -secretase enzyme that cleaves APP resulting in increase in the relative amount of the more amyloidogenic A $\beta$ 42 that is produced. [1] AD is a neurodegenerative condition that causes brain shrinkage and cell death overtime.[2] PSEN2 mutations are reported to be associated with AD of both early onset and variable age onset as well as with other neurodegenerative disorders such as Lewy Body dementia, frontotemporal dementia, Parkinson dementia, and posterior cortical atrophy[2-4].; Patients most often present with an insidious loss of episodic memory followed by a slowly progressive dementia that evolves over years.[3] AD is the most common cause of dementia, which is characterised by a progressive loss of cognitive, behavioural, and social abilities that impairs a person's capacity to operate independently.[1] Dementia is described as a group of symptoms affecting severely to thinking, memory, and social abilities which may interfere with your day-to-day life.[4] AD establishes around 70% of all dementia cases. AD is typically an old age disease. The global prevalence of dementia is about 24 million and it's going to increase 4 times by 2050. AD is expected to cost \$172 billion a year in health-care costs in the United States alone. The incidence rate of AD after the age of 65 is multiplied by 5 times. Age-specific incidence increases significantly from less than 1% per year before 65 years of age to 6% per year after 85 years of age. Prevalence rates increase from 10% after the age of 65 to 40 % after the age of 85. Women are somewhat more likely than males to get AD, especially beyond the age of 85. To date, most validated research results have been narrowed down to yield a model for biological trajectory of AD, where amyloid deposition far precedes clinical symptoms. [5]. Old age and a favourable family history are the two most major risk factors for AD. The prevalence of AD increases with each decade of adult life, reaching 20–40% of the population over the age of 85. A positive family history of dementia

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suggests a genetic contribution to AD, although autosomal dominant inheritance occurs in only 2% of patients. Female sex is a risk factor independent of the greater longevity of women, and women who carry an Apo  $\epsilon 4$  allele are more susceptible than are male  $\epsilon 4$  carriers. A history of head trauma with concussion increases the risk for AD.[2] There are four distinct genetic loci linked to inherited AD risk. Amyloid precursor protein, apolipoprotein E epsilon 4, presenilin 1 and presenilin 2 are four genes that have been linked to hereditary vulnerability to AD. Excessive cerebral amyloid beta plaque buildup and consequent neuronal and glial disease in brain regions crucial for sustaining functions like memory and cognition are caused by mutations or polymorphisms in these genes. Interleukin-1 alpha, interleukin-6, interleukin-10, tumour necrosis factor alpha, cystatin C, neprilysin, angiotensin converting enzyme, BACE 1, cathepsin D, and brain derived neurotrophic factor are some of the other genes linked in AD.[6] There have been relatively few reports utilizing 18F-labelled amyloid beta PET tracers that include clinical implications related to autosomal dominant AD. One study adopted 18F-florbetaben PET imaging in Down syndrome patients, suggesting potential role of amyloid imaging in identifying population at risk of dementia.[6] The major genetic risk factor for AD is apolipoprotein  $\epsilon 4$  (Apo  $\epsilon 4$ ). Carrying one  $\epsilon 4$  allelomorph's increases the risk for AD by 2- to 3-fold, whereas two allelomorph's can increase the risk 16-fold. [2] Microscopic Approach of AD include Neuritic plaques (also known as "senile plaques") are extracellular deposits of the amyloid beta-protein (A $\beta$ ) that are typical microscopic findings of AD. This A $\beta$  alone is found as filamentous masses in the more frequent, smaller diffuse plaques. Similar study was conducted on patients with Down syndrome, but with 18F-florbetapir tracer.[7,8,9]

In AD pathology role of Plaques and tangles are two aberrant formations, are suspected of harming and destroying nerve cells. Plaques are deposits of beta-amyloid, a protein fragment that builds up in the gaps between nerve cells. Tangles are twisted strands of tau, a protein that builds up inside cells.[8] Sign & Symptoms include Having trouble in remembering what just happened, Inability to plan ahead of time or address issue, Not able to remember the seasons, dates, and time, have a habit of misplacing items, Mood swings and personality shifts, Poor decision-making abilities, Having difficulty having discussions, Finding it difficult to speak/find the appropriate words, Issues with vision, Refusal to participate in social or job activities. An attempt to differentiate Down Syndrome pathology from AD has also been made with 18F-florbetapir tracer. [8,10]

In Clinical Examination, Doctors will ask about any changes in person's quality of life and how it is affecting person's ability to perform daily tasks e.g.: - Managing daily hurdles of life, changing cloths, take medication on time, Performing Daily housework. [9] The doctor will inquire about the patient's current and previous medical problems, medicines, and family history of AD or other memory impairments. He or she will also perform a neurologic exam and examine all current vital signs (blood pressure, heart rate, temperature, pulse rate) (check reflexes and coordination, eye movement, speech, and sensation). Testing for mental health. Memory, problem-solving, concentration, counting, and language abilities are among the exams available. This sort of testing can also be used to track AD progression. Neuro psychological evaluations are conducted. Attention, memory, language, planning and reasoning abilities, the capacity to modify behaviour, as well as personality and emotional stability are all assessed in this exam. This sort of testing can also be used to track AD progression. Spine tap is also known as a lumbar puncture, looks for the tau and amyloid proteins that create the plaques and tangles observed in AD patients' brains. Brain Imaging Studies may consist of Computed tomography is a type of brain imaging examination. This scan indicates physical changes in the structure of brain tissue that occur later in AD, such as a reduction in brain size (atrophy), widening of brain tissue indentations, and expansion of the brain's fluid-filled chambers. Magnetic resonance imaging (MRI) is a type of imaging that uses This scan may also reveal signs of brain shrinkage. It can also detect strokes, tumours, fluid accumulation on the brain, and other structural abnormalities that might mimic the symptoms of AD. FMRI stands for functional magnetic resonance imaging (functional MRI). This is a form of MRI that detects variations in blood flow to quantify brain activity in a specific region. Researchers are using this test to understand how the brain changes as AD progresses. It's also being used to test AD therapies before a person develops symptoms. Positron emission tomography (PET SCAN) is a kind of positron emission tomography. The aberrant brain activity in a person with AD may be shown in this scan. It can also aid in the differentiation of AD from other kinds of dementia. PET for Amyloid. The accumulation of amyloid protein in the brain is seen in this scan. PET with FDG. This image tells how efficiently brain cells utilise glucose. AD is characterised by a decrease in glucose absorption.[10] Complications of AD may include Restlessness & Agitation, Bowel & Bladder Problems, Sleeplessness, Mood Swings, Depression, Falls, Infections.[11] In these patients, agitation is widespread and persistent, while psychotic symptoms are less common and only somewhat persistent over time. It's unusual to have a depressed mood with vegetative indications, and it usually doesn't last long. Neuroleptics should be used first for the treatment of psychotic characteristics and agitation.[12] Although there is no cure for AD, one treatment, aducanumab, is the first to indicate that removing amyloid, one of the illness's hallmarks, from the brain can reduce cognitive and functional decline in individuals with early AD. Other treatments can assist persons with AD and their caregivers live better lives by temporarily reducing dementia symptoms and increasing quality of life. There is now a global effort on to find innovative ways to treat, delay, and prevent the sickness from developing.[12].

There are mainly 7 stages for AD. Stage 1 include Normal Outward Behaviour, Stage 2 include Very Mild Changes, Stage 3 include Mild Decline, Stage 4 include Moderate Decline, Stage 5 include Moderately Severe Decline, Stage 6 include Severe Decline, Stage 7 include Very Severe Decline.[13]

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## 2. Management of AD

Approved anti-AD medications: cholinesterase inhibitors and memantine Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and the N-methyl-D-aspartate antagonist, memantine, are the only FDA-approved treatments for AD dementia and are recommended mainly in consensus guidelines and practice variables.[13];Until now, the most widely studied combination drug therapy for AD treatment is the concurrent use of memantine and Cholinesterase inhibitors.[14] Optimal quality of care during the early and middle phases of AD requires the identification of triggers for implementation of Cholinesterase inhibitors and memantine, monitoring of patient response to detect triggers for choosing the pharmacological agent and meet the expectation of patient as well as caregivers.[15] Tacrine is used to treat mild to moderate AD symptoms. Tacrine will not cure AD, nor will it slow down the progression of the illness. In certain Alzheimer's sufferers, tacrine, on the other hand, can help them think more clearly.[16] Donepezil is a drug that is used to treat AD-related disorientation (dementia). In individuals with mild to moderately severe AD, donepezil has been found to be well tolerated and to improve cognition and overall function.[17] The cholinesterase inhibitors donepezil, rivastigmine, and galantamine can delay cognitive impairment in patients with mild to moderately severe AD for at least 6 months duration.[18] Memantine is Uncompetitive antagonist of glutamate receptors of the N-methyl-D-aspartate type. Amantadine treatment resulted in a significant improvement in mental state in three individuals whose autopsy later revealed AD. During the therapy, two patients exhibited a significant improvement. They were able to say a few intelligible sentences when their silent, immobile statuses were reversed.[19]Evidence-based guidelines outlining pharmacotherapeutic strategies can be systematically implemented to optimize outcomes for patients in different stages of AD.[20]

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## 3. Drug information of aducanumab

Aducanumab (ADUHELM) is a monoclonal antibody indicated in the treatment of AD. The recommended dose of ADUHELM is 10 mg/kg IV over 1 hour every 4 weeks and atleast 21 days apart. ADUHELM is a human, immunoglobulin gamma 1(IgG1) monoclonal antibody which reduces aggregated soluble and insoluble amyloid beta plaques in patient with AD.

### 3.1. Adverse drug reaction

Dermatologic ADR include Urticaria Immunologic ADR include Angioedema Neurologic ADR include Magnetic resonance imaging of brain abnormal, Amyloid related imaging abnormalities-edema (35%), Amyloid-related imaging abnormalities-hemosiderin deposition (35%) Side effects may include headache, fall, confusion and diarrhea.

### 3.2. Drug interaction

No interactions were found.

### 3.3. Use in pregnancy and lactation

There are no adequate data on the developmental risk associated with the use of ADUHELM in pregnant women. There are no data on the presence in human milk, effects of on the breastfed infant, or the effects on milk production. Safety and effectiveness in pediatric patients have not been established.

### 3.4. Dose adjustment in organ impairment

No dosage adjustment is needed for patients with renal and hepatic impairment. Also, no specific recommendations are available for geriatric patients. If signs or symptoms of hypersensitivity type of reaction occurs, then promptly discontinue the infusion.

### 3.5. Contraindications

Specific contraindications have not been determined.

### 3.6. Precautions

Neurologic: Use may cause amyloid-related imaging abnormalities-edema (ARIA-E), which may be observed on MRI as brain edema or sulcal effusions, and amyloid-related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. Obtain recent (within 1 year) brain MRI prior to initiation treatment; monitoring is recommended.

Neurologic: The safety of use in patients with any pre-treatment localized superficial siderosis, 10 or more brain microhemorrhages, and/or with a brain hemorrhage greater than 1 cm within 1 year of treatment initiation has not been established.

Immunologic: Angioedema and urticaria has been reported; treatment and prompt discontinuation of therapy may be necessary.

### 3.7. Pharmacokinetics

Absorption by intravenous route 10 mg/kg dose of aducanumab reached a C max of 182.7 µg/mL, with a T max of 3.0 hours, and an AUCinf of 31,400 h\*µg/mL. The volume of distribution of aducanumab is 9.63 L. Metabolism of Aducanumab is expected to be broken down into smaller oligopeptides and amino acids. Route of elimination of Monoclonal IgG is predominantly eliminated by catabolism to individual amino acids that are either recycled in the body or metabolized for energy. The terminal half-life of aducanumab is 24.8 days. A 10 mg/kg intravenous dose of aducanumab has a clearance of 0.39 mL/h/kg.

### 3.8. Effectiveness of aducanumab

Aducanumab dosed at 30 mg/kg was efficacious and well tolerated in the treatment of AD without any potential adverse effects.[21];Aducanumab, is a newer treatment of immunotherapy that can decrease the pathological damage of AD and reverse or slow down the declining of cognitive function for same. [22] A study on effectiveness of aducanumab was done and result shows that it penetrates the brain and anti-beta amyloid concentration decreases with time and dose-dependent manner. After around 15 months of treatment with aducanumab, data shows that 3 mg/kg, 6mg/kg and 10 mg/kg doses show the significant reduction of beta amyloid plaque in patients with AD. They have also conducted a pre-clinical study on rat and administered 30 mg/kg dose via intra-peritoneal route which confronts that 30 mg/kg dose is required for diffusion and closely bound with beta amyloid plaque. In this study, they found some adverse drug reaction like headache, urinary tract infection and upper respiratory tract infection which are related to amyloid-related imaging abnormalities (ARIA).[23] In a Phase I clinical trial, 166 patients with mild prophylaxis or mild symptoms were given 1,3,6, or 10 mg/kg doses of Aducanumab every 4 weeks, and after 54 weeks of treatment, the 3 and 10 mg/kg doses of the drug significantly reduced Ab content in the brain and improved cognitive ability, with the higher dose being more pronounced, compared to placebo. Although the findings of the 6 mg/kg dose group did not differ from those of the 3 mg/kg and 10 mg/kg dose groups, the dose of 6 mg/kg was able to dramatically lower Ab levels in the brain, slowing the patient's mental decline. [23]. Aducanumab can also be used with scanning ultrasound for not only improves cognitive functions but also reduce the beta amyloid plaque load. They found that aducanumab analogue or scanning ultrasound alone can reduce beta amyloid plaque load, but combination therapy has an additional effect on improving cognitive function which is confirmed by active place avoidance (APA) test. 24] All the other patient's, who received 60 mg/kg aducanumab has developed systemic adverse drug reaction, which are symptomatic amyloid-related imaging abnormalities (SARI). These were also completely reversed by 2-3 months.[22] Amyloid protein clumps in the brain (plaques) are a neuropathological feature of Alzheimer's disease and widely assumed to trigger a cascade of changes that cause cognitive decline. Aducanumab is a monoclonal antibody that removes amyloid plaques[24]

The study was conducted to found out long-term effects of aducanumab, which shows positive outcome with almost less or no potent adverse effect, which makes this molecule a ray of hope for the patients of AD. Some see aducanumab as proof of concept for the amyloid cascade theory, justifying decades of unsuccessful research costing billions of pounds and exposing thousands of participants to the side effects of experimental treatments. Others fear it will simply encourage futile investment in anti-amyloid therapies, diverting funds away from effective prevention measures such as improving physical activity or reducing hypertension [25]

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## 4. Conclusion

AD is the leading cause of impairment among those over the age of 60. In India, about a million cases are recorded each year. Is a monoclonal antibody, which is a novel type of medicine used to treat AD. Aducanumab a the first ever disease modifying drug and new medication that treats the fundamental cause of AD, however it has some controversies on its

efficacy and approval but has been demonstrated in recent trials to be effective and safe for Alzheimer's patients. Genetic counseling may be required in some circumstances, and all patients and care partners require education and support. Building this infrastructure for the appropriate use of aducanumab will require time, resources, and creative planning. Appropriate use of aducanumab requires a commitment to patient-centered care and best-practices for the safe delivery of this new treatment.

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## Compliance with ethical standards

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No conflict of interest existed between authors.

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