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Aducanumab: A Potential Magic Bullet for Alzheimer's Disease?

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Abstract

Aducanumab (BIIB037) is a high-affinity, fully human IgG1 monoclonal antibody against amyloid-beta (Aβ). Aβ plays a significant role in the pathophysiology of Alzheimer's disease (AD). The antibody was developed through a screening of libraries of human memory B cells for reactivity against aggregated Aβ that led to the molecular cloning, sequencing, and recombinant expression of the drug. The preferential binding of the antibody to the aggregated forms of Aβ, including soluble oligomers andinsoluble fibrils, could slow down the progression of AD. Preclinical studies in mice proved that aducanumab selectively binds to the parenchymal amyloid over vascular amyloid, decreasing plaques of all sizes. Studies have also found that there were no new amyloid-related imaging abnormalities (ARIAs) when monitored with Magnetic resonance imaging (MRI) scans. Aducanumab's proven ability to penetrate and accumulate in the brain tissue reduced the amyloid loads. Aducanumab efficacy is dependent on dose and apolipoprotein E4 (ApoE4) status. There are significant side effects like edema and in some cases, hemorrhage has been reported. Currently, Biogen has completed two Phase 3 trials, ENGAGE (NCT02477800) and EMERGE (NCT02484547), in the United States and other countries. To this day, no antibody-based immunotherapies targeting Aβ are available in the market for treatment of AD.

Keywords: *Aducanumab; Alzheimer's Disease; Amyloid Beta; Monoclonal Antibody*

Abbreviations

AD: Alzheimer's Disease; Aβ: Amyloid Beta

Background

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder leading to disability in the elderly population. The disease can soon become a global epidemic, because there are no treatments available to prevent the progression of AD. The current medications may help to treat symptoms. The World Health Organization (WHO) reports the most common form of dementia is AD and includes 60 - 70% of dementias affecting 47.5 billion people in 2015. For patients greater than 65 years old, the worldwide incidence doubles every five years for AD [1]. According to Drug candidates in clinical trials for Alzheimer's disease, as the average age of the population increases, there will be an increase in AD patients and will be tripled by 2050, estimating over 115 million people. There is also an increase in cost for helping patients with AD, which is second to cancer care, costing the US economy $172 billion every year [1]. Dementia is prevalent in older adults, and according to Medicare data, 19% of seniors who die in a given year, are diagnosed with AD [2].

Alzheimer's disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks. Two fundamental neuropathological mechanisms are contributing to the pathogenesis for AD. The first mechanism includes extracellular amyloid-β (Aβ) peptide deposition causing senile plaques (SPs). The second mechanism involves the formation of intracellular neurofibrillary tangles (NFTs) with hyperphosphorylated tau protein [3]. Although there are two potential mechanisms, the formation of SPs contributes to the process of developing NFTs. Aβ peptides include about 38 - 42 amino acids generated by a sequential cleavage of amyloid precursor protein (APP), which is a type 1 transmembrane protein, by β-secretase (BACE) and γ-secretases [3]. There are 42 Aβ residues (Aβ1-42) that are more likely to create fibrils and SPs. Genetic mutations in both the amyloid precursor protein (APP) and the presenilin (PSEN) genes cause familial Alzheimer's disease (FAD) with autosomal dominant inheritance and early onset of disease. Aβ42 plays a significant role in tau pathogenesis and cognitive impairment. Presenilins contribute to the γ-secretase complexes by cleaving APP in the transmembrane to create Aβ42 peptide. The correlation between BACE and γ-secretase led to a theory known as the "amyloid cascade hypothesis". This theory shows that Aβ42 production and aggregation causes AD because of the relation between β and γ-secretases. When there is an accumulation of Aβ42 (soluble oligomers and protofibrils), it becomes highly toxic [4]. These aggregations of Aβ42 can later become insoluble fibers and break off, leading to the formation of amyloid plaques. Neuropathological changes in AD includes acetylcholine deficiency, glutamate excitotoxicity, neuroinflammation, and neuronal loss [1].

Currently, there are limited medications available to help manage symptoms of AD. FDA approved treatments include acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and NMDA antagonist (memantine) or their combination[5]. The currently available medications do not slow down or prevent the progression of the disease, but only treat symptoms. Donepezil is used in mild to severe AD, whereas memantine is used for moderate to severe AD. The remaining medications are only used in mild to moderate AD. These medications do not cure AD but help to improve cognitive function.

Much of the research has done to slow down the progression of AD, especially at the early stages of AD. The most advanced strategy for treating AD is the enhancement of Aβ clearance by passive immunotherapy. Bapineuzumab, a humanized form of a murine monoclonal antibody that binds the N-terminal epitope Aβ, was terminated due to a lack of efficacy in mild to moderate AD. Later, Solanezumab, a monoclonal antibody, was designed to target Aβ16-24. This antibody attacks soluble monomeric Aβ and not fibrillaryAβ. Solanezumab was discontinued as it failed to accomplish the primary endpoint in clinical studies [1].

Aducanumab (BIIB037) is a high-affinity, fully human IgG1 monoclonal antibody against amyloid-beta (Aβ) [6]. This medication was studied in donors who were aged and had normal cognition. The studies of antibodies had led to the process called "reverse translational medicine" [7-9]. Aducanumab binds explicitly to an aggregated form of Aβ by binding to parenchymal beta-amyloid over vascular amyloid. In a 13-week study in mice, the results showed decreased plaques in all sizes, but the vascular amyloid levels unchanged. The only adverse effect reported was micro-hemorrhages when giving aducanumab at 500 mg/kg, which was higher dose than the minimal effective dose for plaque reduction.

Since the currently available medications do not stop disease progression, aducanumab perhaps be indicated for AD as one of the first-line treatments, primarily to slow down the progression of AD. According to the U.S. Food and Drug Administration (FDA), Biogen (makers of aducanumab) has been granted Fast Track designation because of the preclinical studies outcome.

Preclinical pharmacology

Aducanumab was designed and developed to inhibit the growth of amyloid-beta, and is unique because of its high-affinity binding. Figure 1 shows the mechanism of Aducanumab. Aducanumab acts by specifically working on the Aβ oligomers and including fibrils and plaques. Aducanumab has dual effects of decreasing Aβ42 that causes AD and also preventing the inflammatory responses of tauaggregation and tangle s , which results in the edcline o f t he sy na ps e a n d neurons. The development of aducanu m a b was used as an antibody-based immunotherapeutic approach. Aducanumab was created by selecting human B-cell clones triggered by epitopes in Aβ aggregates. The human memory B cells reactivity against the aggregated Aβ led to molecular cloning, sequencing and recombinant

expression of BIIB037. The amyloid hypothesis of Aβ toxicity that causes synaptic dysfunction and neurodegeneration is the main underlying cause of progression in AD. There has been a lack of success in other studies due to the selectivity of Aβ [6].

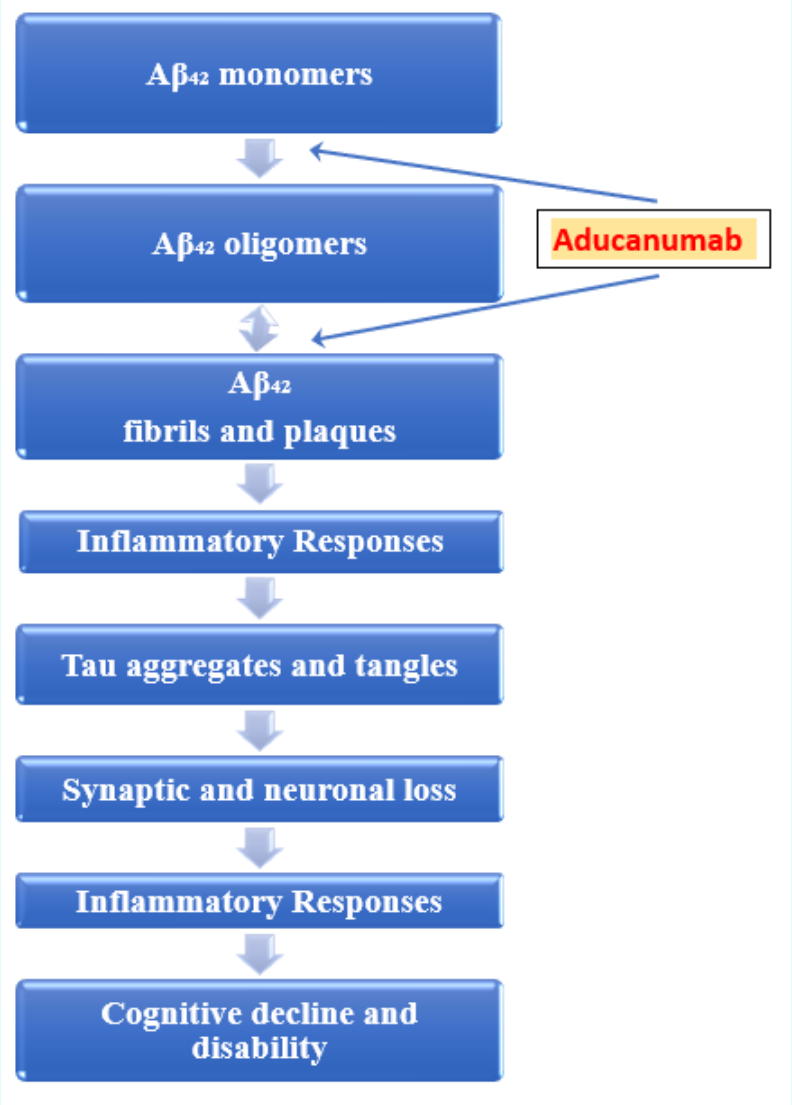

Figure 1: *Potential mechanism of aducanumab.*

In preclinical studies, Aducanumab is capable of crossing the blood-brain barrier and specifically binds to the target. This will allow the clearance of Aβ from plaque accumulation in mouse brains. Treatment with Aducanumab decreased the Aβ plaques in a dose and time-dependent fashion as measured by florbetapir PET imaging [6]. Aducanumab efficacy is also dependent on apolipoprotein E4.

Pharmacokinetics and metabolism

The pharmacokinetics of Aducanumab are linear for maximum concentration (Cmax) and cumulative area under the concentration curve (AUC). The median plasma half-life is 21 days. During a study, about 3% (3 out of 118) patients developed treatmentemergent anti-Aducanumab antibodies within the first year of treatment. There were minimal titrations and no significant changes in pharmacokinetics.

In the PRIME preclinical studies, Aducanumab was given as a single dose of 30 mg/kg intraperitoneally. Administration of a single dose did not affect the plasma or brain. In 24-hour dosing, aducanumab was bound to parenchymal brain Aβ.

Safety

The most common adverse effects were amyloid-related imaging abnormalities (ARIA), headache, urinary tract infection, diarrhea, and upper respiratory infection. ARIA was observed in patients who received 60 mg/kg, and one of the patients was not APOe4 noncarrier (symptomatic ARIA-E and ARIA-H non-symptomatic). Other adverse effects experienced in the ARIA-E patients were moderate cognitive disorder, headache, pyrexia, and severe pain. These side effects were resolved within 1 - 2 days. There were no cases of ARIA in aducanumab doses of ≤ 30 mg/kg [4]. The terminal elimination half-life, volume distribution, and mean clearance were not affected by increasing doses [10].

Clinical studies

Phase 1 studies were conducted to assess the safety and pharmacokinetics of BIIB037 with a dose of 0.3 mg/kg intravenous injection in patients with mild to moderate AD. The results of this study showed a decrease in ARIAs monitored with four MRI scans. Side effects consisted of headache, diarrhea and dizziness. No new ARIA developed during the trial. As 30 mg/kg was efficacious with mild to moderate side effects, a further dose was added at 60 mg/kg [7-9]. This study showed the efficacy of the drug without any plasma spike. Biogen started PRIME, a multicenter, multiple-dose study in patients with mild AD. Patients were to score more than 19 on the minimental state examination (MMSE), 0.5 to 1 on the Clinical Dementia Rating, and less than 27 on the Free and Cued Selective Reminding Test (FCSRT) before entering the study. The study analyzed amyloid PET and MRI scans for confirmation of amyloid in patients. Since the test patients did no produce any false positives, Biogen moved into a Phase 3 trial. Interim data analysis indicated aducanumab dose-dependently reduced amyloid deposition significantly in six cortical regions of the brain. Side effects of ARIA-E, headache, and confusion were reported. Aducanumab reduced the decline on the MMSE and CDR-SB scores. The PRIME study continued until 2016, even after these results showed improvement in AD. After one year of analysis, 6 mg/kg dose of aducanumab reduced brain amyloid and continued to have a slow decline in the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) scores. After these results, the Phase 1 study was started in Japan with a dose of 6 mg/kg. Phase 3 began immediately with two efficacy trials in the united states and other countries in the year 2015 known as ENGAGE (NCT02477800) and EMERGE (NCT02484547). These studies enrolled thousands of people with MCI due to AD or mild AD with positive amyloid on a PET scan.

On March 21, 2019, Biogen and Eisai announced they would terminate all ongoing aducanumab trials, following an interim analysis that predicted EMERGE and ENGAGE would miss their primary endpoints. On October 22, 2019, Biogen announced the interim futility analysis was wrong, and that subsequent analysis of a more substantial data set instead showed EMERGE had met its primary endpoint. Participants on the highest dose of 10 mg/kg had a significant reduction in decline on the primary endpoint, the CDR-SB. The low-dose group had some slowing of progression, but the differences were not statistically significant from placebo.

The ENGAGE trial did not meet the primary endpoint; however, an exploratory analysis suggested that a subgroup of people who hadreceived 10 or more than 10 mg/kg doses declined more slowly, similar to comparable EMERGE participants. In sub-studies to these trials, aducanumab caused a dose-dependent reduction in brain amyloid and some CSF phospho-Tau reduction. As in prior trials, the

most common adverse effects were ARIA-E and headache. Based on interactions with the FDA, Biogen announced plans to apply in early 2020 for regulatory approval for aducanumab in the U.S [11].

Mechanism-based classification		Name	Developer	Current status
Anti-amyloid strategies	Aβ vaccination	AN1792	Elan	Discontinued
		CAD106	Novartis	Phase 2/3, being tested in API generation
		ACI-24	AC immune	Phase 1/2
		ABvac40	Araclon Biotech	Phase 2
		Affitope AD02	Affilis AG	Phase 2
		ACC-001	Janssen	Discontinued
	Anti-Aβ antibodies	Bapineuzumab	Pfizer, Janssen	Discontinued
		Gantenerumab	Roche/Chugai	Phase 3, being tested in DIAN-TU
		Crenezumab	Genentech/AC immune/ Roche	Phase 3, being tested in API-ADAD
		Solanezumab	Eli Lilly	Phase 3
		Aducanumab	Biogen	Phase 3
	γ-secretase inhibitor	Semagacestat	Eli Lilly	Discontinued
	Notch-sparing γ-secretase inhibitor	Avagacestat	Bristol-Myers Squibb	Discontinued
	γ-secretase modulator	Tarenflurbil	Myriad Genetics and Laboratories	Discontinued
		CHF5074	CereSpir™ Incorporated/ Chiesi Pharmaceuticals Inc.	Phase 2
		PF-06648671	Pfizer	Phase 1
	β-secretase inhibitor	LY2811376	Eli Lilly	Discontinued
		LY2886721	Eli Lilly	Discontinued
		MK-8931 (Verubacestat)	Merck	Phase 3
		AZD3293/LY3314814	AstraZeneka/Eli Lilly	Phase 2/3
		CNP520	Novartis/Amgen	Phase 2/3, being tested in API generation
		E2609 (Elenbecestat)	Eisai/Biogen	Phase 3
		JNJ-54861911	Janssen	Phase 3 (EARLY trial)
Anti-tau strategies	Tau aggregation inhibitor	LMTM (TRx0237)	TauRx Therapeutics Ltd	Phase 3
	Tau kinase inhibitor	Lithium	University of Dundee	Phase 3
		NP031112 (Tideglusib)	Noscira	Discontinued
	Active vaccination for tau	ACI-35	AC immune/Jansen	Phase 1b
		AAD-vac1	Axon Neuroscience SE	Phase 2

Table 1: *Disease-modifying therapies for AD under clinical development [12].*

Conclusion

Aducanumab is an injectable antibody that reduces Aβ plaques in the brain. By lowering the Aβ plaques, aducanumab can prevent the progression of AD substantially compared to other therapies. Although there is a risk of ARIA-E, it was only shown with very high doses of aducanumab. This injectable drug will allow maintaining the quality of life for patients with AD, especially at the early stages. Since this medication is dose-dependent, there is less stress over toxicity. Aducanumab is also a monthly intravenous infusion that may slow down the progression of AD. The medication enters the brain and binds to parenchymal Aβ to reduce soluble and insoluble Aβ in patients with mild AD. Although the antibody drug therapies are at the beginning of making an impact on AD, there is a need for medications that prevent the progression of the disease. Currently, there are no FDA approved therapies that are known to halt or slow the progression of AD but only help treat symptoms. If approved by FDA, aducanumab will be the first disease-modifying therapy for Alzheimer's Disease.

Conflict of Interest

None.

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