Monoclonal Antibodies Against Amyloid Beta in the Treatment of Early Alzheimer's Disease

USC Mann
Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences

Sharon Park, Tanjia Toma, Brian Tran, Phitsini Treenate
Project Advisor: Enrique Cadenas, MD, PhD

Project ID: 714

Introduction/Background

AD is a fatal neurodegenerative disease that primarily affects elderly population over the age of 60. AD is characterized by progressive cognitive decline, including impaired memory, judgment, problem-solving, and attention span. One of the hallmark pathological features of AD is the accumulation of amyloid beta (Aβ) species in the brain which are neurotoxic peptides that are byproducts of amyloid precursor protein (APP) metabolism in the brain. The balance of Aβ production and clearance is lost in patients with AD, resulting in an accumulation of Aβ. Despite extensive research, exact mechanisms underlying AD development and progression remain unclear.

There is currently no cure for AD, and existing treatments only offer limited symptomatic relief and may delay disease progression. Aducanumab can clear Aβ plaques by selectively binding amyloid aggregates in both oligomeric and fibrillar states rather than amyloid monomers alone. Lecanemab is a humanized IgG1 monoclonal antibody that targets soluble Aβ aggregates with activity across oligomers, protofibrils, and insoluble fibrils. Unlike the first two drugs that have been FDA approved, Donanemab is a phase 3 trial drug that is still undergoing FDA approval but has shown to significantly slow cognitive and functional decline in people living with early symptomatic AD. Donanemab is a humanized IgG1 monoclonal antibody that recognizes Aβ(p3-42) that is aggregated in amyloid plaques. Although aducanumab, Lecanemab and Donanemab are all monoclonal antibodies, they work differently by targeting beta-amyloid at different stages of plaque formation to reduce Aβ aggregates and improve cognitive function.

This literature review assesses the efficacy of the three monoclonal antibodies in the treatment of early AD. Primary outcome is the reduction of beta-amyloid plaques in relation to cognition improvement. Patient demographics and consequential comorbidities are taken into account during this review in the attempt to generalize treatment approach guidelines.

Objective

To evaluate the efficacy of Aducanumab, Donanemab, and Lecanemab in treating early Alzheimer's disease as demonstrated by reduction of beta amyloid plaques and subsequent improvement in cognition. Secondary objective is to assess whether data results can be potentially applied to the general population or if it is population-specific.

Methods

A literature review was performed utilizing PubMed. The terms Aducanumab, Lecanemab, Donanemab, and Alzheimer's were used for the initial search. Additional filters applied to narrow down the search include articles published within the past 5 years, randomized control trials, and clinical trials. This yielded 767 articles, of which 744 were excluded to account for article duplication and the applied search filters. Duplicated articles were identified and removed using Endnote automatic remover. The remaining 23 articles were reviewed and resulted in a total of 4 articles being analyzed since 19 articles were reviews of the 4 primary articles mentioned above.

Article inclusion criteria when reviewing the literature include the following: patients diagnosed with early AD from apparent mild cognitive impairment (MCI), MMSE:20 to 30 (normal-mild), MoCA: 6-25 (mild-moderate), and age ≥ 50.

Article exclusion criteria were as follows: patients who have other neurodegenerative diseases or cognitive impairment due to causes other than AD (i.e. stroke, autoimmune disorders, tumors), age <50 yrs, patients with moderate-severe cognition (MMSE of 0-19 and MoCA: less than 6), articles published over 5 years ago, meta analysis, and reviews.

Data

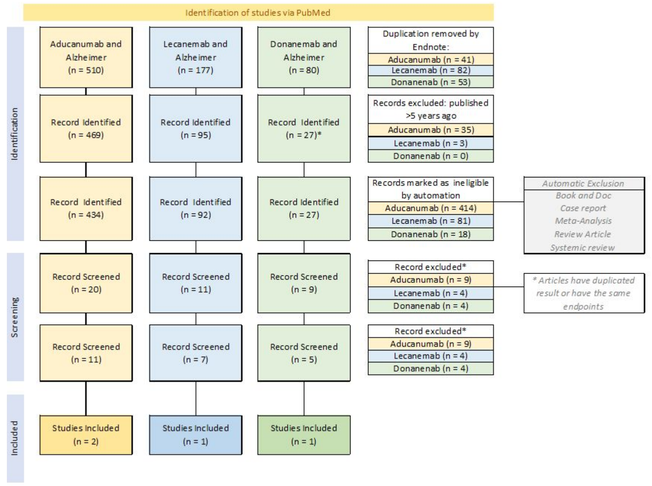


Figure 1. Literature search flow chart.

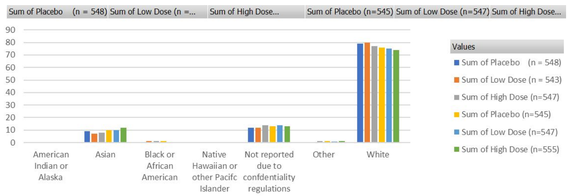
		Aducanemab				Lecanemab	Donanemab	
		EMERGE		ENGAGE		CLARITY-AD**	TRAILBLAZER-ALZ2***	
	Scale Type	Low-Dose vs Placebo	High-Dose vs Placebo	Low-Dose vs Placebo	High-Dose vs Placebo	Lecanemab vs Placebo	Low/Medium tau vs Placebo	Combined vs Placebo
Primary Endpoint	CDR-SB	-15%	-22%	-12%	2%	-27%	-	-
	iADRS	-	-	-	-	-	35.1%	22.3%
	Amyloid PET Changes	-0.165 centiloid (SUVR*)	-0.278 centiloid (SUVR*)	-0.168 centiloid (SUVR*)	-0.232 centiloid (SUVR*)	-59.12 centiloids	-87.0 centiloids	-88.0 centiloids
Secondary Endpoint	MMSE	3%	-18%	-6%	3%	-	-	-
	CDR-SB	-	-	-	-	-	-36%	-28.9%

SUVR: Standardized Uptake Value Ratio

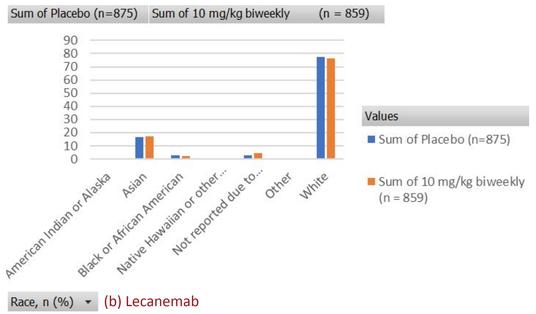
Table 1. Cross-comparison of primary and secondary endpoints among the hallmark trials. EMERGE and ENGAGE data are interpreted as reduction in amyloid-beta. CLARITY-AD** data are interpreted as disease progression is n% slower than placebo. TRAILBLAZER-ALZ2*** data interpreted as n% more efficacious than placebo in slowly disease progression.

Table 2. Patient population characteristics across the hallmark trials (EMERGE, ENGAGE, CLARITY-AD, and TRAILBLAZER-ALZ2).

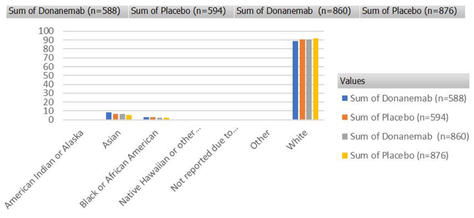
	Aducanumab						Lecanemab		Donanemab			
	EMERGE			ENGAGE			CLARITY-AD		TRAILBLAZER-ALZ2			
									Low/Medium tau		Combined tau	
Characteristic	Placebo (n = 548)	Low Dose (n = 543)	High Dose (n=547)	Placebo (n=545)	Low Dose (n=547)	High Dose (n=555)	Placebo (n=875)	10 mg/kg biweekly (n = 859)	Donanemab (n=588)	Placebo (n=594)	Donanemab (n=860)	Placebo (n=876)
Age, mean ± SD, years	70.8±7.4	70.6±7.4	70.6±7.5	69.8±7.7	70.4±7.0	70.0±7.7	71.0 (7.8)	71.4 (7.9)	74.3 ± 5.7	74.3 ± 5.8	73.0 ± 6.2	73.0 ± 6.2
Sex												
Male, n (%)	47%	50%	48%	47%	48%	47%	411 (47.0 %)	416 (48.4%)	263 (44.7%)	273 (46.0%)	367 (42.7%)	373 (42.6%)
Female, n (%)	53%	50%	52%	53%	52%	53%	464 (53.0%)	443 (51.6%)	325 (55.3%)	321 (54.0%)	493 (57.3%)	503 (57.4%)
Race, n (%)												
American Indian or Alaska	1 (0.2%)	0 (0%)	0(0%)	0 (0%)	0(0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)	2 (0.2%)	0 (0%)
Asian	47 (9%)	39 (7%)	42 (8%)	55 (10%)	55 (10%)	65 (12%)	148 (16.9%)	147 (17.1%)	48 (8.2%)	38 (6.4%)	57 (6.6%)	47 (5.4%)
Black or African American	1 (0.2%)	6 (1%)	4 (1%)	5 (1%)	1 (0.2%)	2 (0.4%)	24 (2.7%)	20 (2.3%)	17 (2.9%)	17 (2.9%)	19 (2.2%)	21 (2.4%)
White	431 (79%)	432 (80%)	422 (77%)	413 (76%)	412 (75%)	413 (74%)	677 (77.4%)	655 (76.3%)	522 (88.8%)	539 (90.7%)	781 (90.9%)	807 (92.1%)
Not reported due to confdentiality regulations	67 (12%)	65 (12%)	75 (14%)	69 (13%)	74 (14%)	72 (13%)	26 (3.0%)	37 (4.3%)	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)
Other	1 (0.2%)	1 (0.2%)	3 (1%)	3 (1%)	4 (0.7%)	3 (1%)			0 (0%)	0 (0%)	0 (0%)	1 (0.1%)



(a) Aducanumab



(b) Lecanemab



(c) Donanemab

Figures 2a-c. Patient population demographics in the hallmark trials.

Results

The two main Aducanumab studies were ENGAGE and EMERGE. The primary outcome was to measure the change from baseline using the Clinical Dementia Rating Sum of Boxes (CDR-SB). In EMERGE, there was a significant reduction of 22% in the high dose compared to the placebo. However, ENGAGE demonstrated a 2% increase in the aducanumab group which resulted in the study not meeting its primary or secondary endpoints. Furthermore, amyloid PET scans showed a -.278 and -.232 centiloid reduction in amyloid plaques in Emerge and Engage respectively. Adverse reactions (ADRs) were similar between treatments groups but overall higher with aducanumab. Both trials were halted based on futility analysis after 76 weeks from half of the participants.

In TRAILBLAZER-ALZ2, CDR-SB scores were lower by 36% and 29% in Donanemab compared to placebo for low/medium tau population and for combined tau population, respectively. Additionally, amyloid PET scan showed a -87 and -88 centiloids reduction in plaques in the low/medium tau population and combined group respectively. On the other hand, signs of edema or effusion occurred in 24% of the participants receiving Donanemab compared to 2.1% receiving placebo

CLARITY-AD showed a 27% reduction in CDR-SB score in the treatment (Lecanemab) group compared to the placebo. Furthermore, amyloid PET scan showed a -55.4 centiloids reduction in amyloid plaques in the treatment arm compared to placebo. Serious ADRs occurred in 14% of the treatment group and 11.3% of the placebo group.

Discussion

Aducanumab, donanemab and lecanemab mostly demonstrated reductions in CDR-SB scores. The use of randomization and blinding helped internal validity of the studies, but was also threaten as each drug was sponsored by their respective Pharma company. Although the results from each of these trials were significant, they cannot be generalized or used in a standardized practice due to several limitations. All three clinical trials consisted of at least 70% white population, underrepresenting Asians, Blacks, Hispanics and other ethnicities. As a consequence, the drugs cannot be deemed effective because there is no clinically significant evidence of the drugs being efficacious in a large heterogeneous patient population. Furthermore, the trials consisted of a relatively small group of participants with shorter duration of follow-up, which threatens the external validities of these studies. Surprisingly, recent news this year showed Biogen removing the drug aducanumab (Aduhelm) from the drug market do to insufficient results from the EMERGE and ENGAGE trials. In EMERGE, 40% of participants did not finish the study, a harm on internal validity. Also, ENGAGE shows no significant changes in CDR-SB in the high-dose group. Further studies that include a larger and more heterogeneous population are needed in order to evaluate true efficacy and amyloid beta sensitivity in a general population.

References

1. Budd Haeberlein, S et al. "Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease." *The journal of prevention of Alzheimer's disease* vol. 9,2 (2022): 197-210. doi:10.14283/jpad.2022.30
2. Sims, John R et al. "Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial." *JAMA* vol. 330,6 (2023): 512-527. doi:10.1001/jama.2023.13239
3. van Dyck, Christopher H et al. "Lecanemab in Early Alzheimer's Disease." *The New England journal of medicine* vol. 388,1 (2023): 9-21. doi:10.1056/NEJMoa2212948

Note: This is an incomplete list of references. Other references can be provided if needed

Acknowledgement

Thank you to the USC Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences. We would like to acknowledge our scholarly project advisor, Dr. Enrique Cadenas, for his support and guidance throughout this project.