A Comparison on Efficacy Data for Monoclonal Antibodies and Cholinesterase Inhibitors for Treatment of Alzheimer's Disease from the FDA Medical and Statistical Reports

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INTRODUCTION

Despite extensive research into therapeutic options for Alzheimer's Disease (AD), as of now two classes of medications are approved; cholinesterase inhibitors (AChEIs) and monoclonal antibodies (mAb). There is considerable debate around the efficacy profile of the newer monoclonal medications, specifically in comparison to the older medications [1]. Because of this gap in literature, we evaluated the efficacy, mortality and morbidity risk among the seven FDA approved medications [2], in the context that the efficacy with monoclonal antibodies is higher. We hypothesized that monoclonal antibodies indicated for Alzheimer's disease would show a greater decrease in ADAS-Cog scores in comparison to cholinesterase inhibitors and placebo.

METHODS

We searched the FDA database (www.accessdata.fda.gov/scripts/cder/daf/index) for all approved AD treatment drugs through January 2025, focusing on verified efficacy data for investigational medications. Our search targeted cholinesterase inhibitors (memantine, donepezil, galantamine, rivastigmine) and monoclonal antibodies (lecanemab, aducanumab, donanemab).

Inclusion Criteria: Availability of both drug and placebo groups in randomized clinical trials, an ADAS-Cog scale used as either a primary or secondary endpoint for patients diagnosed with AD of varying severity, approved doses, and discontinued medications

Exclusion Criteria: Extension trials, and studies involving participants with other neurological conditions (e.g., Parkinson's Disease).

New Drug Applications (NDAs) are formal, standardized submissions to the U.S. Food and Drug Administration (FDA) that include independently reviewed data on a drug's safety, efficacy, and manufacturing quality. NDAs represent the final regulatory step for marketing approval following clinical trials.

From the FDA database, five unique medications met our criteria, yielding a total of 10 trials and 9,614 participants (see Table 1).

We extracted demographic information (sample sizes, age, sex, and race) along with ADAS-Cog scale versions, baseline scores, and end-of-treatment scores. To evaluate treatment efficacy, we calculated the difference in mean change from baseline between drug and placebo arms.

RESULTS

Table 1 summarizes the number of trial participants, percentage of female and Caucasian participants, average age, and study duration for each trial. Demographic variables such as age, sex, and race, were generally consistent across studies. Notably, trials involving monoclonal antibodies were nearly twice as long in duration compared to studies evaluating cholinesterase inhibitors.

Table 1: Demographic Characteristics among 9,614 Trial Participants in Trials for Monoclonal Antibodies and Cholinesterase Inhibitors, Based on the Efficacy Database.

Drug	n	% Female	% Caucasian	Age ± SD	Study Duration, weeks
Donanemab					76
Placebo	876	57.4	92.1	n/a	
Drug	860	57.3	90.8	n/a	
Lecanemab					78
Placebo	875	53	77.4	71 (7.8)	
Drug	859	51.6	76.3	71.4 (7.9)	
Aducanemab					78
Placebo	1093	52.8	77.2	70.3 (7.5)	
Drug	2192	51.5	76.6	70.4 (7.4)	
Donepezil					24
Placebo	315	62.3	95	73	
Drug	315	62.3	95	73	
Galantamine					29
Placebo	832	60.6	95.8	73.4 ± 85.3	
Drug	1397	61.3	95.5	74 ± 59.9	

n/a: not available

Table 2 reports the scale, baseline scores, mean change from baseline, and the difference between mean change between drug and placebo arms.

Table 2: Comparison of ADAS-Cog Scale Versions, Baseline Cognitive Scores, and Treatment Effects of Monoclonal Antibodies and Cholinesterase Inhibitors

	Scale	Baseline Scores		Mean Change from Baseline		Mean Change Drug - Placebo
		Drug	*Placebo*	*Drug*	*Placebo*	
Donanemab	Adas-Cog13	28.5 ± 8.9	29.2 ± 8.9	4.2	5.3	-1.1
Lecanemab	Adas-Cog14	24.4 ± 7.6	24.5 ± 7.1	4.14	5.6	-1.46
Aducanemab	Adas-Cog13	22.4	22.2	4.3	5.2	-0.8
Donepezil	Adas-Cog (unspecified)	26.6 ± 8.7	26.4 ± 7.7	-1.62	1.17	-2.79
Galantamine	Adas-Cog11	26.2 ± 69	25.9 ± 91.2	-0.6	2.21	-2.81

SUMMARY

This study aimed to examine and compare the cognitive efficacy outcomes of monoclonal antibodies (mAbs) and cholinesterase inhibitors (AChEIs) using data from randomized controlled trials submitted to the FDA. ADAS-Cog scores were used as a primary outcome across all included trials. Baseline cognitive scores across both drug classes were relatively comparable, suggesting that trial participants began with similar levels of cognitive impairment within each disease stage. Contrary to our hypothesis, after analysis we found that the cholinesterase inhibitors showed a greater mean difference from placebo in ADAS-Cog scores than monoclonal antibodies.

Donepezil and galantamine exhibited a drug-placebo difference of -2.79 and -2.81 points, respectively, whereas donanenemab, lecanemab, and aducanemab showed differences of only -1.1, -1.46, and -0.8, respectively. Although all drugs demonstrated statistically significant improvement compared to placebo in within their trials, the magnitude of cognitive benefit as measured by ADAS-Cog appeared more pronounced among trials for cholinesterase inhibitors. However, we should keep in mind that the length of the studies in weeks was significantly lower for cholinesterase inhibitors compared to monoclonal antibodies. These findings may raise questions about the relative clinical impact of newer therapies like monoclonal antibodies, particularly when viewed through the lens of cognitive scales like ADAS-Cog but we should only draw conclusions based on studies done for similar durations.

Limitations

The two drug classes, monoclonal antibodies and cholinesterase inhibitors, are indicated for different stages of Alzheimer's disease. Monoclonal antibodies are primarily studied and prescribed for patients with mild cognitive impairment or early Alzheimer's disease.

Cholinesterase inhibitors are often used in patients with moderate to severe Alzheimer's disease. The degree of cognitive change that can be expected may differ based on disease stage.

The trails examined here used different versions of the ADAS-Cog scale (e.g., ADAS-Cog 11, 13, or 14). This heterogeneity in measurement tools complicates direct efficacy comparisons across studies.

Differences in study duration, sample demographics, and trial design further limit the generalizability of results.

As mAbs gain regulatory approval and are used in early Alzheimer's disease management, future research should focus on standardized outcome measures that can more sensitively detect early cognitive changes and allow for direct comparison across therapeutic classes.

CONCLUSION

All drugs showed a statistically significant difference ADAS-Cog scores relative to placebo. However, mAbs are tested and approved for Mild Cognitive Impairment (MCI) or mild dementia. On the other hand, AChEIs were tested and approved for moderate to severe AD.

Since these studies employed different versions of the ADAS-Cog scale (e.g., ADAS-Cog 11 vs. ADAS-Cog 13), making direct comparisons of efficacy more difficult. Additional research is needed to fully assess the efficacy of these newer therapies compared to placebo

REFERENCES

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