Cumulative cognitive benefits and brain volume change with anti- amyloid therapies for Alzheimer's disease

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Abstract

Objective This study aimed to evaluate the cumulative benefits of Food and Drug Administration (FDA)-approved monoclonal antibodies (mABs), administered at FDA-approved dosing regimens in slowing cognitive decline compared with placebo and acetylcholinesterase inhibitor (AChEI), and the dynamic relationships between cognitive decline, amyloid reduction and whole brain volume (WBV) changes in mAB treatment.

Methods Five major databases were systematically searched for double-blinded randomised controlled trials of patients with mild cognitive impairment due to Alzheimer's disease (AD) or mild AD treated with mAB or AChEI for at least 6 months. The primary outcomes were the change in cognitive function measured by Alzheimer's Disease Assessment Scale—cognitive subscale 14-Item (ADAS-Cog) and Clinical Dementia Rating Scale—Sum of Boxes (CDR-SOB). The secondary outcomes included amyloid burden and WBV changes.

Results There were 6479 participants across seven mAB trials, and 4993 participants in nine AChEI trials. Compared with placebo, the pooled percentage of cognitive slowing was 27.6% (95% CI 24.6% to 30.9%), and the pooled progression delay was 5.52 months over 19.5 months (1.40 to 9.65) on CDR-SOB in patients treated with mABs. For cognitive trajectories on ADAS-Cog, mAB progressively attenuated cognitive decline, whereas AChEI exhibited a smaller effect with large uncertainty and eventually provided no benefits. Additionally, the rates of cognitive decline and amyloid reduction stabilised over time, while WBV initially showed a rapid decline but progressively slowed. Finally, WBV decline was not associated with worsening cognitive function. Instead, a 1 cm^3 reduction in WBV was linked to a 0.0975-point reduction in CDR-SOB (0.0614 to 0.1336).

Conclusions In prodromal to mild AD, mAB therapy provided greater cumulative cognitive benefits than placebo and AChEI, and WBV reduction may reflect a treatment-related process rather than a detrimental sequela.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

- The US Food and Drug Administration recently approved monoclonal antibodies (mAB) targeting β-amyloid plaques as disease-modifying therapies for Alzheimer's disease (AD). In clinical trials, mAB treatment has been associated with amyloid reduction and whole brain volume (WBV) loss. However, the relationship with amyloid reduction, WBV loss and cognitive function preservation remains unclear. Moreover, the cumulative benefits of mAB therapy in slowing cognitive decline compared with acetylcholinesterase inhibitors (AChEIs) have not been examined.

WHAT THIS STUDY ADDS

- Our findings suggested that mAB therapy demonstrated greater efficacy in slowing cognitive decline compared with placebo (5.52 months pooled progression delay over 19.5 months). When compared with AChEI, mAB progressively attenuated cognitive decline, whereas AChEI exhibited a smaller effect with large uncertainty and provided no benefit. Both amyloid reduction and WBV loss stabilised over time and correlated with cognitive benefits rather than impairment.
- In the prodromal to mild AD, mAB therapy provided greater cumulative cognitive benefits than placebo and AChEI. The observed WBV loss during mAB therapy may reflect a treatment-related process rather than a detrimental sequela.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This study highlights the cumulative cognitive benefits of monoclonal antibody therapy over AChEIs in early AD, supporting its use as a disease-modifying approach rather than purely symptomatic treatment. The findings also suggest that WBV loss during treatment may represent a therapeutic effect rather than neurodegeneration, which could inform future biomarker interpretation and clinical trial design.

Introduction

Acetylcholinesterase inhibitor (AChEI) has been approved as the first-line pharmacological treatment for reducing symptoms of Alzheimer's disease (AD) over the past 20–30 years.[1] The US Food and Drug Administration (FDA) recently approved three monoclonal antibodies (mABs), namely aducanumab, lecanemab and donanemab targeting β-amyloid plaques as disease-modifying therapies for mild cognitive impairment (MCI) due to AD or mild AD.[2 3] However, several challenges have emerged.

A key challenge is quantifying the cumulative cognitive benefits of mAB therapy versus placebo using disease progression models. This includes three metrics: the percentage of cognitive slowing and progression delay, the latter of which measures the time preserved after mAB treatment.[4 5] This is particularly important because mAbs are claimed to be disease-modifying treatments, yet they demonstrate minimal effect sizes in attenuating cognitive decline despite significantly reducing amyloid levels on positron emission tomography (PET) imaging. They should demonstrate longer survival time (cognition preservation) than standard symptomatic treatment with AChEI.[6] A second challenge is the observation of greater brain volume loss with mAB treatment compared with placebo in mAB trials, noting that some degree of volume loss is expected over time in AD.[7–9] Brain atrophy due to neuronal loss may compromise long-term brain health and is unlikely to contribute to slowing cognitive decline. This raises concerns about whether such changes reflect beneficial amyloid-β clearance, ongoing neurodegeneration or other unintended effects,[10] while amyloid-removal-related pseudo-atrophy has been suggested.[11] A third challenge lies in determining the extent to which amyloid-β clearance translates to cognitive preservation. Previous studies, such as those by Ackley *et al* [12] and Pang *et al*,[13] attempted to quantify this relationship by examining the cognitive benefits associated with a 0.1-unit reduction in amyloid-β. However, these analyses included failed mAB drugs, non-mAB therapies and treatments across different AD stages, limiting the applicability of their findings to currently approved mAB therapies.

The major aim of this study is to accurately quantify the cumulative benefits of mAB in slowing cognitive decline compared with placebo and AChEI. Given concerns that mAB-associated brain volume loss may diminish therapeutic benefits, the second aim is to investigate the dynamic relationships among cumulative cognitive benefit, amyloid reduction and brain volume changes over time. Finally, we examined whether whole brain volume (WBV) loss correlates with changes in cognitive decline and amyloid reduction. This analysis provides valuable insights into how amyloid reduction, cognitive benefits and brain volume changes interact over time during mAB treatment.

To ensure transparency regarding related work, we have recently published a related systematic review and meta-analysis comparing anti-amyloid mABs with AChEIs, which focused primarily on the magnitude of treatment effects on conventional cognitive

scales and subgroup analyses across genotypes and disease stages.[14] In contrast, the present study addresses distinct research questions and applies analyses. Specifically, we quantify longitudinal disease-modifying signals by estimating cognitive slowing and progression delay, and we evaluate the relationships among dynamic cognitive trajectories, amyloid biomarker changes and longitudinal neuroimaging outcomes (including WBV change) under anti-amyloid therapy. Accordingly, although some underlying trial literature may overlap, the objectives, endpoints and inferences of the present work are different, and the neuroimaging-focused analyses constitute the primary novel contribution of this study.

Methods

The study protocol has been registered in advance on PROSPERO. The study is reported following the Preferred Reporting Items for Systematic Review and Meta-analysis statement online supplemental appendix 1.[15]

Eligibility criteria

The inclusion criteria required studies to be double-blinded randomised controlled trials (RCTs) enrolling patients at the prodromal to mild stages of AD, defined as MCI due to AD or mild AD. Eligible studies needed to evaluate treatments with FDA-approved mABs or AChEIs in comparison to placebo, with a minimum treatment duration of 24 weeks. Studies were excluded if they were non-randomised, focused on other types of dementia (eg, vascular dementia), or lacked clear specification of the AD stage. Additional exclusion criteria included studies reporting only pharmacodynamic or pharmacokinetic outcomes, studies involving patients with moderate or severe AD or MCI due to non-AD aetiologies and studies that did not report primary outcomes.

Search strategy and study selection

Two reviewers independently searched the PubMed, Cochrane Central Register of Controlled Trials, Embase, PsycINFO and ClinicalTrial.gov databases without language restrictions from database inception to 15 December 2024. Manual searches of reference lists of included studies and other systematic reviews were undertaken to identify additional studies. Two reviewers independently screened titles, abstracts and full-text articles of selected records to confirm eligibility. Title, abstract and full-text screening required agreement between reviewers. Reviewers resolved disagreements by discussion and, if necessary, by consultation with a third senior author. Appendix 2 shows the complete search strategies, and Appendix 3 presents the reasons for exclusion.

Outcomes and data extraction

The primary outcome was cognitive function, measured through two validated assessment tools: the Alzheimer's Disease Assessment Scale—cognitive subscale 14-

Item (ADAS-Cog) and the Clinical Dementia Rating Scale—Sum of Boxes (CDR-SOB). To ensure standardisation, different versions of ADAS-Cog (such as 11-item or 13-item) were converted to the 14-Item version using validated methods.[16] The secondary outcomes included amyloid burden and WBV. Amyloid burden was quantified through the standardised uptake value ratio (SUVR) derived from amyloid PET imaging, which reflects the extent of amyloid deposition in the brain. WBV was assessed using MRI, providing a structural measurement of brain atrophy and volume changes over time. To ensure accuracy of the data collected, two reviewers independently extracted data using standardised and pre-piloted extraction forms. Data were extracted from intention-to-treat or last observation carried forward analyses, along with estimates from mixed-effect models for repeated measures. Numerical data from figures were extracted using WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/). For both mAB and AChEI trials, only data from FDA-approved recommended doses were included.

Risk of bias (ROB) assessment

Following a similar approach to the data extraction process, two authors independently assessed the ROB for the primary outcomes of the included RCTs. We used the Cochrane Risk of Bias Tool for randomised trials V.2.0,[17] with any discrepancies resolved through consensus discussion and, when necessary, by consulting a third reviewer.

Data synthesis

All analyses were performed using R (V.4.2.2) with the nlme, dosresmeta, meta and dplyr packages. For both primary and secondary outcomes, we calculated the mean difference (95% CI) as the change from baseline in the treatment group (mAB or AChEI) minus that of the placebo group. To model cognitive measures over time, for mAB trials, we conducted a one-stage, random-effects dose-response meta-analysis using restricted maximum likelihood estimation[18] with restricted cubic spline models (three knots set at 10th, 50th and 90th percentiles, per Harrell's recommendation).[19] We assessed the efficacy on slowing cognitive decline using two metrics: (1) Percentage of cognitive slowing: this quantifies how much cognitive decline was reduced by treatment compared with placebo. For each study, we calculated the difference in decline between the treatment and placebo groups, then expressed it as a percentage of the placebo group's decline. These results were combined using random-effects meta-analysis. Higher percentages indicate greater efficacy in slowing cognitive decline. (2) Progression delay: This measures how much sooner it takes for the placebo group to reach the level of cognitive decline as the treatment group. In each study, we estimated the cognitive trajectories of both treatment and placebo groups and calculated the time difference (in months) at which they reached the same decline.

The progression delay metric requires that the cognitive trajectories of the treatment and placebo groups remain parallel over time in each study, without substantial

divergence or reversal. To verify this assumption, we visually inspected the between-group difference curves and applied two tests (treatment endpoint within placebo range and local monotonicity around crossing). A detailed methodology is provided in Appendix 4. These two metrics were then pooled using random-effects meta-analysis with the Knapp-Hartung adjustment and profile-likelihood CIs for between-study variance. Heterogeneity was measured by I^2, and substantial heterogeneity was further examined using leave-one-out sensitivity analysis.

To examine the temporal relationships between cognitive decline, amyloid reduction and WBV loss, we conducted a two-phase analysis. First, we used fractional polynomials, selected based on Akaike information criterion and adjusted R-squared, to determine the optimal time-scaling function for each outcome. This approach identified linear patterns for cognitive measures, a square root function for amyloid reduction and a cubic pattern for WBV changes. Second, based on these non-linear relationships, we estimated the rate of change over time using mixed-effects models with variance weighting to account for between-study heterogeneity.

Amyloid accumulation, brain atrophy and cognitive decline represent key interconnected pathways in AD progression. We specifically examined their relationships to better understand the mechanisms underlying treatment effects. However, although these studies were RCTs, the number of participants with amyloid and WBV measurements was substantially lower than those with cognitive assessments, raising concerns about unmeasured confounding factors. To address potential biases from differential missing data, we conducted instrumental variable meta-analysis (IVMA) using randomisation as the instrumental variable.[12 13] IVMA allowed us to quantify: (1) the effect of amyloid reduction on slowing cognitive decline, (2) the association between amyloid reduction and WBV loss and (3) the association between WBV loss and slowing cognitive decline. Detailed statistical analysis methods are provided in Appendix 4, while the reasons for protocol changes are described in Appendix 5.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of this study because it was a systematic review and meta-analysis of aggregated, de-identified clinical trial data. We plan to disseminate the findings to clinicians and lay audiences through academic presentations, lectures and social media. Dissemination to participants and related patient and public communities: Dissemination of the work to the public and clinical community through social media and lectures is planned.

Results

Characteristics of the included studies

After searching the database and excluding duplicated records, we identified 3360 unique potential studies. We then screened the titles and abstracts of these studies for eligibility and excluded 3126 of them, in which 234 studies remained. 224 studies were excluded after an assessment of the full text for various reasons (Appendix 3). We identified four additional studies through a manual search, resulting in a total of 14 eligible studies(online supplemental figure 1. Details of the characteristics of the included studies are shown in etable 1. Overall, 6479 people (mean age of 71.5 years, 53.4% (3366/6309) were women) were included in mABs trials (7 trials, 6 articles),[7–9 20–22] and 4993 participants (mean age of 70.7 years, 56.8% (2748/4839) were women) were included in AChEI trials (9 trials, 8 articles).[23–30]

Risk of bias

No mAB trial (0/7) was judged to be at high overall ROB (eFigures 2 and 3). All seven mAB trials were rated as low ROB across all five RoB 2 domains (randomisation, deviations from intended interventions, missing outcome data, outcome measurement and selection of the reported result).

Similarly, no AChEI trial (0/9) was rated as high overall ROB. All nine AChEI trials were judged to have low ROB for randomisation and outcome measurement, whereas some concerns were noted for deviations from intended interventions and missing outcome data in one trial each (1/9). In contrast, selection of the reported result raised some concerns in most AChEI trials (7/9), with the remaining two trials (2/9) rated as low risk in this domain.

Cumulative cognitive benefit of mAB

Figure 1 shows the cumulative cognitive benefit of mAB compared with placebo. After 19.5 months of mAB therapy, the pooled percentage of cognitive slowing was 25.6% (17.6% to 37.2%; I^2=0%; efigure 4) on ADAS-Cog and 27.6% (24.6% to 30.9%; I^2=0%; efigure 5) on CDR-SOB. The pooled progression delay was 3.67 months (2.20 to 5.14; I^2=40%; efigure 6) on ADAS-Cog and 5.52 months (1.40 to 9.65; I^2=93%; efigure 7) on CDR-SOB over 19.5 months. The substantial heterogeneity of progression delay on CDR-SOB might be derived from the study by Haeberlein *et al* (2022) (efigure 8).

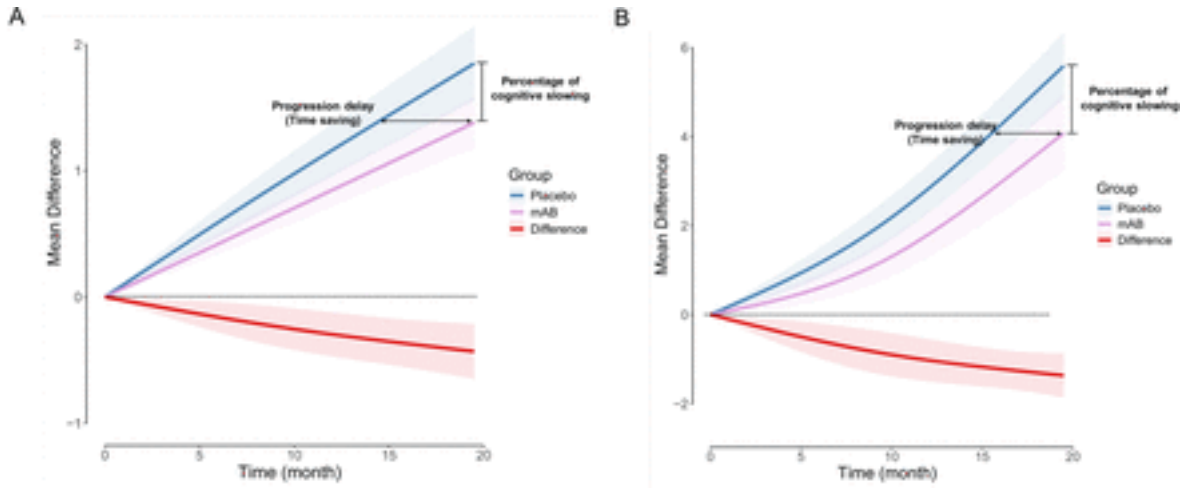

Figure 1. The efficacy of cumulative cognitive benefits for (A) ADAS-Cog and (B) CDR-SOB. ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item; CDR-SOB, Clinical Dementia Rating Scale Sum of Boxes; mAB, anti-amyloid beta monoclonal antibody.

Visual comparison of mAB with AChEI on cumulative cognitive benefit

On both the ADAS-Cog and CDR-SOB assessments (figure 2A and B), mAB progressively slowed cognitive decline compared with placebo, with the difference between mAB and placebo becoming larger over time. In contrast, AChEI showed a smaller and more gradual effect, with a trajectory that remained closer to placebo. Notably, in ADAS-Cog, the AChEI versus placebo difference eventually became negative (figure 2A). The pooled percentage of cognitive slowing and the pooled progression delay of AChEI compared with placebo could not be estimated (Appendix 4), because the AChEI and placebo groups showed highly divergent trends, non-parallel trajectories or crossing curves (efigures 9–10). Therefore, we used pairwise meta-analyses to examine the mean difference of AChEI compared with placebo on ADAS-Cog (−0.24, 95% CI −1.22 to 0.73; I^2=76%; efigure 11) and CDR-SOB (−0.11, 95% CI −0.22 to −0.002; I^2=0%; efigure 12). For mAB compared with placebo, the pooled mean difference was −1.27 (−1.69 to −0.84; I^2=0%; efigure 13) on ADAS-Cog and −0.41 (−0.62 to −0.20; I^2=56%; efigure 14) on CDR-SOB.

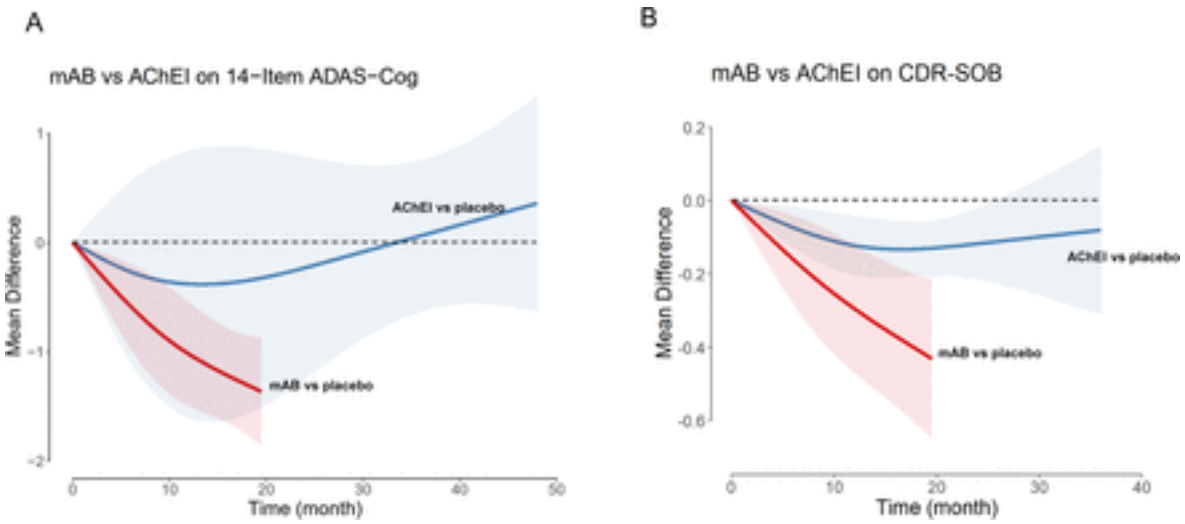

Figure 2. Comparisons of cumulative cognitive benefits between mABs versus AChEIs on (A) ADAS-Cog and (B) CDR-SOB. AChEI, acetylcholinesterase inhibitor; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item; CDR-SOB, Clinical Dementia Rating Scale Sum of Boxes; mAB, anti-amyloid beta monoclonal antibody.

Temporal relationship between cognitive function, amyloid burden and WBV

The estimated rate of change for the CDR-SOB, ADAS-Cog, amyloid reduction and WBV loss is shown in figure 3. For CDR-SOB, the estimated rate continued to decrease and reached −0.52 (95% CI −0.82 to −0.22) at the last time window. For ADAS-Cog, the rate was −1.60 (95% CI −2.66 to −0.54) at the last time window. The amyloid reduction demonstrated a steady decline, stabilising at −0.43 (95% CI −0.82 to −0.22) at the last time window. However, for WBV, the rate of change started at −9.39 and showed a slower rate of decline over time, stabilising to −2.83 (95% CI −5.07 to −0.59) at the last time window. The results of fractional polynomials and the pairwise meta-analyses of amyloid reduction and WBV loss are shown in efigures 15–17.

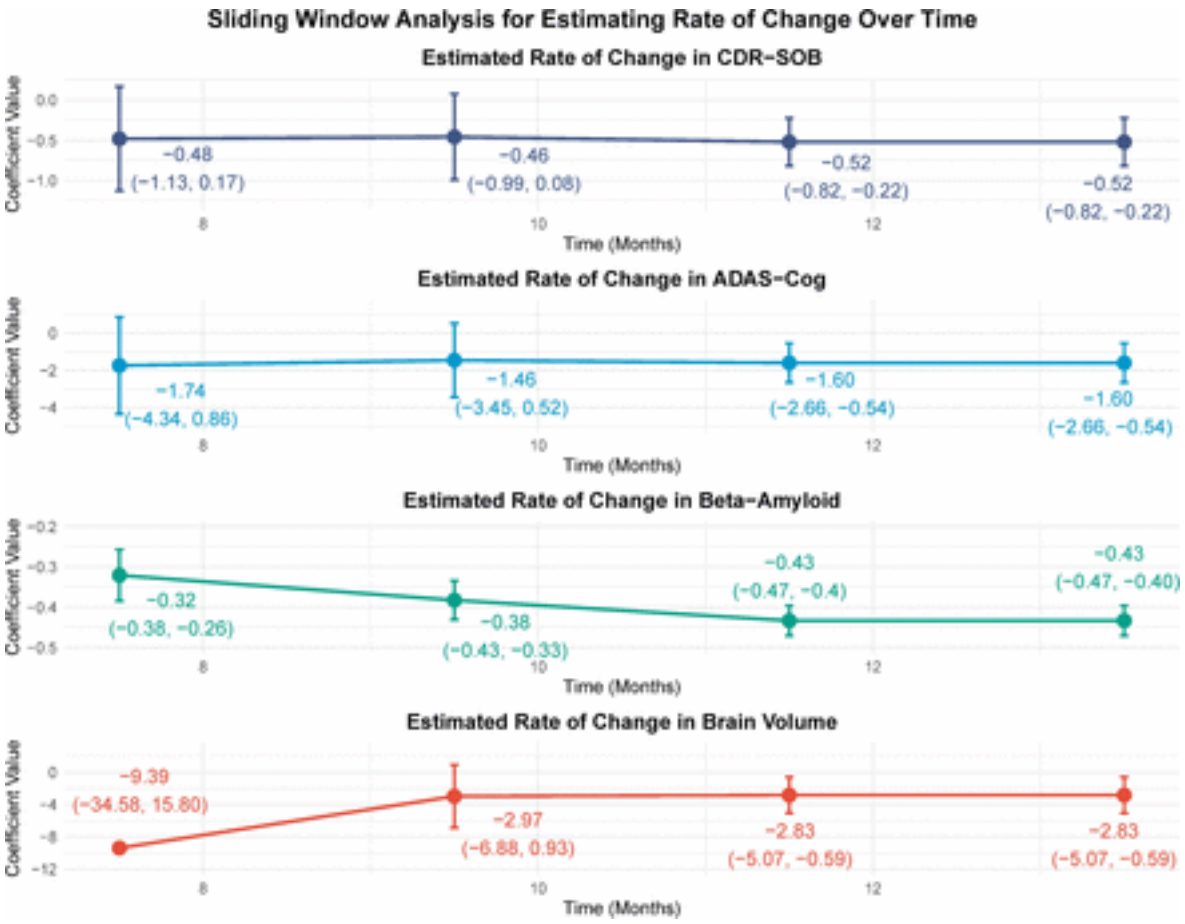

Figure 3. Estimated annual rate of change in cognition, amyloid burden and brain volume. ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item; CDR-SOB, Clinical Dementia Rating Scale Sum of Boxes.

IVMA for potential causal association

The results of the IVMA demonstrated that a 0.1-unit reduction in PET amyloid beta SUVR was associated with a 0.1165-point reduction in cognitive decline as measured by CDR-SOB (95% CI 0.0829 to 0.1500) (figure 4). Additionally, WBV decline was not associated with worsening cognitive function. Instead, a 1 cm^3 reduction in WBV was linked to a 0.0975-point reduction in cognitive decline on CDR-SOB (95% CI 0.0614 to 0.1336). Finally, a 1 cm^3 decline in WBV was associated with a 0.1-unit reduction in PET amyloid beta SUVR.

Figure 4. IVMA estimates of the potential causal association between amyloid reduction, whole brain volume decline and CDR-SOB change. CDR-SOB, Clinical Dementia Rating Scale Sum of Boxes; IVMA, instrumental variable meta-analysis; SUVR, positron emission tomography-measured Aβ standardised uptake value ratio.

Discussion

Principal finding

This study found that, compared with placebo, mAB may delay the progression of cognitive decline by 4–5 months over 19.5 months of treatment, with a 26%–27% cognitive slowing estimates from the ADAS-Cog and CDR-SOB assessments. Additionally, the cumulative cognitive benefits of mAB were better than those of AChEI. The temporal analysis showed that the rates of cognitive decline and amyloid reduction both stabilised over time, indicating consistent and sustained treatment benefits. In contrast, WBV loss initially shows a rapid decline but progressively slows, reflecting a distinct temporal dynamic compared with the other measures. Finally, the WBV loss might not be associated with worsening cognitive function, but correlated to cognitive function benefit and amyloid reduction.

Comparison with other studies

In our study, mAB demonstrated significant cumulative benefits by preserving more time compared with placebo, indicating slower progression of cognitive decline. Furthermore, mAB showed greater cumulative cognitive benefits compared with AChEI over approximately 2 years of treatment. In our leave-one-out analysis, we found that the Haeberlein *et al* (2022) (ENGAGE) was the heterogeneity source.[7] The phase 3 trials EMERGE and ENGAGE of aducanumab produced inconsistent outcomes, with only EMERGE showing a post hoc high-dose benefit while ENGAGE failed to meet its primary endpoint. This discrepancy likely resulted from differences in high-dose exposure due to mid-trial protocol changes, early discontinuation and random baseline variation rather than a reproducible therapeutic effect.[31] A previous cohort study using data from the National Alzheimer's Coordinating Centre reported that patients with mild to moderate

AD treated with AChEI experienced a smaller decline in Mini-Mental Status Examination score (5.7 vs 10.8) over 12 years.[32] To ensure a level playing field when indirectly comparing mAB trials with AChEI trials, we deliberately restricted the AChEI evidence base to early AD and excluded trials enrolling mild-to-moderate or later-stage dementia (eg, the 24-week donepezil study by Rogers *et al*),[33] where faster baseline decline can inflate the apparent absolute treatment gain. Notably, demonstrating benefit in earlier disease stages is intrinsically more challenging because placebo decline is smaller, so an equivalent percentage slowing translates into a smaller absolute difference on cognitive scales. For illustration, our pooled AChEI effects versus placebo were modest (−0.24 on ADAS-Cog and −0.11 on CDR-SOB), whereas the donepezil study by Rogers *et al* in patients with CDR global 1–2 reported larger absolute benefits (2.9 on ADAS-Cog and 0.6 on CDR-SOB). This contrast likely reflects differences in disease stage, baseline trajectory and trial design/endpoint timing, underscoring why later-stage AChEI trials were excluded from the indirect comparison despite their larger absolute changes. On the other hand, our study using RCT data showed that AChEI was initially more effective than placebo in slowing cognitive decline, while its efficacy diminished over time and fell below placebo by 40 months on ADAS-Cog. Our findings addressed whether mABs, compared with AChEIs, can further extend survival time (in terms of slowing cognitive decline), although through indirect comparison.[6] Unfortunately, there is still a lack of direct comparison (head-to-head RCT) evidence. Although some scholars have questioned the hypothesis that Aβ is the central cause of the disease,[34–36] long-term use of mABs (around 20 months) has shown that, in addition to clearing amyloid plaques, mABs still have a positive effect on preserving cognitive function. It is worth noting that mABs and the amyloid-β hypothesis still face scepticism, particularly regarding the reduced effectiveness of mABs in patients who are APOE-4 carriers.[20 22 34 37 38] APOE-4 is a well-known risk factor for AD and is believed to be associated with Aβ pathology.[39]

Although WBV loss was observed following mAB therapy, this phenomenon should be interpreted within a broader context. Several scholars have questioned whether mAB-related brain volume loss is a warning sign of neuronal damage rather than merely a result of amyloid plaque removal.[34 40–42] In this study, WBV initially declined rapidly but gradually slowed and eventually stabilised over time, suggesting a self-limiting adaptive process rather than progressive pathological atrophy. Notably, during this period, continuous amyloid clearance was observed alongside sustained cognitive benefits. If the WBV loss represented harmful atrophy, concurrent attenuation in cognitive decline would not be plausible. Indeed, our IVMA revealed a 0.0975-point reduction in CDR-SOB per 1 cm^3 reduction in WBV. Importantly, we specifically addressed the potential co-linearity between amyloid removal and WBV loss to validate this finding. We distinguished their effects by first observing their distinct temporal trajectories (square-root vs cubic patterns). Furthermore, the IVMA confirmed that treatment-associated WBV reduction was not associated with cognitive decline, but rather independently

linked to cognitive improvement. Collectively, this evidence supports the conclusion that changes in WBV are likely a normal adaptive phenomenon during the treatment process, rather than a harmful atrophic process—at least from the perspective of cognitive function.

Several mechanisms have been proposed to explain the WBV reduction with mAB treatment. First, the direct physical impact is that β-amyloid plaques are cleared. Previous studies suggested that β-amyloid plaques occupy approximately 6%–8% of cortical grey matter in post-mortem brains of AD, equivalent to around 2%–3% of total brain volume.[11 43] The second mechanism is the attenuation of the cellular response to aggregated β-amyloid. Increased microglial activity is proposed as a key driver of plaque clearance.[44] Once β-amyloid is cleared, microglia may disperse and reduce their activity. Histological studies on patients treated with AN1792 showed that the percentage of cortical area occupied by microglia was halved compared with untreated AD patients.[45] These changes may directly or indirectly contribute to the volume reduction observed on MRI.[11]

Strengths and limitations of this study

Our study has several limitations. First, most AChEI trials were published between 2000 and 2010, while the mAB trials were published after 2020. Advances in trial methodology might contribute to more stable treatment trajectories observed in the mAB trials. Second, the inclusion criteria were different between these two types of RCTs. For example, in the AChEI trials, amyloid-PET or equivalent biomarkers were not required to confirm the diagnosis of AD, which might contribute to treatment heterogeneity in AChEI trials. Third, because of the limited number of mAB trials, we could not conduct subgroup analyses for sex and Apolipoprotein E4 genotype.[46] RCTs have shown that the cognitive effects of lecanemab and donanemab are less favourable for APOE4 homozygous carriers compared with non-carriers.[20 22] Finally, the cumulative benefits of mAB observed in RCTs may underestimate real-world effectiveness, because the absolute benefits of mAB treatment are observed without the need for comparison in real-world settings.

Implications and conclusions

Although our study found that mAb therapy was associated with greater cumulative benefits compared with AChEI treatment, these findings should be interpreted in the context of differences in patient populations between the two treatment groups. We also found that amyloid burden was cleared at a steady rate and correlated with slowing cognitive decline during mAB therapy. The mAB-associated WBV loss was not linked to worsening cognitive function but was instead associated with cognitive benefits and amyloid reduction. These findings offer valuable insights into the dynamic relationships among cognitive function, amyloid-beta burden and WBV.

Ethics approval

E-DA Hospital institutional review board approved the study protocol (2025018) and waived the requirement for informed consent since this investigation used aggregated identified clinical trial data, and no human subjects contact was required.

Acknowledgments

We wish to transparently disclose that our group has recently published a related systematic review and meta-analysis in the Journal of Prevention of Alzheimer's Disease (JPAD) evaluating anti-amyloid monoclonal antibodies in comparison with acetylcholinesterase inhibitors, focusing primarily on the magnitude of treatment effects on conventional cognitive scale outcomes and subgroup analyses across genotypes and disease stages. The present manuscript addresses distinct research questions and includes analyses that were not reported in the JPAD publication. Specifically, here we quantify longitudinal disease-modifying signals by estimating cognitive slowing and progression delay, and we further examine the relationships among dynamic cognitive trajectories, amyloid biomarker changes and longitudinal neuroimaging outcomes (including brain volume change) with anti-amyloid therapies. Accordingly, while the underlying trial literature may partially overlap, the analytical aims, endpoints and inferences of the present work are different, and the neuroimaging-focused findings are emphasised as the primary novel contribution of this manuscript. Dissemination to participants and related patient and public communities: We plan to disseminate the findings of this study to lay audiences through mainstream and social media.

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