Monoclonal Antibodies for the Treatment of Prodromal Alzheimer's Disease

Katrina Grunst, PA-S

Background & Purpose

- Alzheimer's disease (AD) is characterized by a progressive loss of cognitive functioning ability, ultimately leading to severe dementia and loss of basic motor functioning.
- AD patients account for a large percentage of healthcare expenditures.[1]
- With the geriatric population expanding, the rates of AD is expected to rise significantly.[2]
- Monoclonal antibody therapy is being studied in clinical trials as a treatment that may possibly delay or even reverse cognitive decline in AD patients.

This research aims to explore the efficacy and safety of these new drug treatments that may alter the underlying process of AD and potentially prevent cognitive decline in future generations.

PICOT

In patients with prodromal Alzheimer's disease, does treatment with monoclonal antibodies (aducanumab, lecanemab, and gantenerumab) show increased cognitive functioning compared to placebo after approximately two years of treatment?

Design & Methods

•**Keywords:** Alzheimer's disease, dementia, monoclonal antibody, disease-modifying drugs, amyloid-beta, aducanumab, lecanemab, gantenerumab
•**Inclusion:** Studies comparing monoclonal antibodies to placebo, focusing on patients with mild-moderate AD, published within the last five years, and available in English.
•**Exclusion:** Studies focusing on severe AD or other forms of dementia, published over five years ago, lacking placebo controls, or assessing primary outcomes outside of cognitive functioning or neurologic amyloid-beta concentrations.

Summary of Evidence Search

Database	Yielded	Reviewed	Included in Analysis
Google Scholar	563	26	12
PubMed	345	11	6
Total:	908	37	18

Synthesis of Evidence

- Systematic reviews/Meta-analyses - 4
- Randomized controlled studies - 9
- Interim analysis sub-study- 1
- Other - 4

Results

- Aducanumab reduced the rate of functional and cognitive decline in patients with mild AD, showing improvements in CDR-SB, ADAS-Cog13, and ADCS-ADL scores.[3]
- Lecanemab demonstrated overall success in cognitive outcomes, with less decline in CDR-SB and improvements in ADAS-Cog14 and ADCS-MCI-ADL scores, and delayed dementia progression.[4]
- Gantenerumab showed no significant clinical benefit, though subgroup analysis indicated a dose-dependent response in cognitive decline, especially in fast progressors.[5]
- Safety concerns include the risk of amyloid-related imaging abnormalities-effusion (ARIA-E), highest with aducanumab, and noted with lecanemab and gantenerumab, though ARIA events were mostly manageable, allowing continued treatment at lower doses.[3-5]

Tool	Aducanumab[3]	Lecanemab[4]	Gantenerumab[5]
Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) Range: 1-18	MD: -0.39	WMD: -0.45	MD: -0.08
Mini Mental State Examination (MMSE) Range: 0-30	MD: 0.6	N/A	MD: -0.31
Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) Range: 0-53	MD: 1.7	N/A	MD: 0.95
Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog13) Range: 0-85	MD: -1.400	WMD: -1.11	MD: -1.05
Amyloid Burden on PETSUVr	MD: -0.272	WMD: -0.15	SMD: -1.06

Discussion

- Most clinical trials have shown a positive correlation between the drug treatment and its ability to reduce amyloid-beta plaques in the brain, delaying cognitive decline, and improving daily living activities in AD patients.
- Further research with broader applicability for advanced stage dementias and improvement in safety profiles is necessary.

Limitations

- Small number of trials analyzed
- Potential publication bias
- Outdated cognitive assessment scales
- Aducanumab trial initially halted due to low likelihood of reaching primary endpoints
- Gantenerumab trials terminated early for futility
- APOE-genotype correlated results

Conclusion

In conclusion, anti-amyloid monoclonal antibodies show promise in slowing cognitive decline in early AD. Still, the exclusive focus on amyloid-beta plaques raises questions about alternative treatment routes. Clarifying the clinical significance of amyloid-beta reduction and exploring alternative therapies while continuing further research on these medications are crucial for advancing AD treatment. While their efficacy in advanced stages is still uncertain, their utilization in clinical practice could make vast changes to the disease outcomes.

References:

1. Norins LC. Predicted economic damage from a quick, simple Alzheimer's disease cure. *Medical Hypotheses*. 2019;133:109398. doi:10.1016/j.mehy.2019.109398
2. Alzheimer's Disease Facts and Figures. Alzheimer's Disease and Dementia. Accessed April 28, 2024. https://www.alz.org/alzheimers-dementia/facts-figures
3. Haddad HW, Malone GW, Comardelle NJ, Degueure AE, Kaye AM, Kaye AD. Aducanumab, a Novel Anti-Amyloid Monoclonal Antibody, for the Treatment of Alzheimer's Disease: A Comprehensive Review. *Health Psychol Res*. 10(1):31925. doi:10.52965/001c.31925
4. Qiao Y, Chi Y, Zhang Q, Ma Y. Safety and efficacy of lecanemab for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials. *Frontiers in Aging Neuroscience*. 2023;15. Accessed December 3, 2023. https://www.frontiersin.org/articles/10.3389/fnagi.2023.1169499
5. Sobral MVS, Soares VG, Gonçalves OR, et al. Efficacy and safety of gantenerumab in the treatment of Alzheimer's disease: A meta-analysis of randomized controlled trials. *Archives of Gerontology and Geriatrics Plus*. 2024;1(2):100016. doi:10.1016/j.aggp.2024.100016

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