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Anti-amyloid agents for treating incipient Alzheimer's disease: a new hope?

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The aims of current therapeutic drugs for Alzheimer's disease (AD) are to restore the cognitive and functional capacity of individuals to some extent, while preserving autonomy and quality of life. Although important, clinical practice has shown that these objectives are insufficient. Future perspectives indicate more ambitious directions, such as halting neurodegeneration by modifying the disease's natural history. Continuing efforts toward disease-modifying AD treatments have led to the (albeit controversial) approval of aducanumab in July 2021 by the U.S. FDA. The anti-amyloid agents developed in the last few years have reinforced the "amyloid cascade" hypothesis as the main pathological pathway underlying the disease. However, the fact that most of these agents have failed to demonstrate significant benefits has led researchers to question whether the amyloid theoretical model is sufficient.

Currently, 126 registered therapeutic agents are being studied for AD treatment. These include agents developed based on a myriad of pathways and pathological models, such as oxidative stress, gut-brain axis, vasculature, inflammation, tau, and obviously, amyloid. On the amyloid front there are two main strategies: passive and active immunotherapy.¹ Researchers have had better success with agents that follow the passive immunotherapy strategy. The main objective of these agents is to reduce the brain amyloid burden using exogenous monoclonal antibodies directed at different portions of the amyloid- β (A β) peptide, i.e., monomers, oligomers, protofibrils, and fibrils. The agents developed so far are expensive and require multiple injections. However, these treatments can be promptly interrupted when adverse events occur.² Some of these agents have successfully removed amyloid- β from the brain parenchyma, although the concurrent removal of amyloid- β from vessels has led to vasogenic edema and microbleeding, as observed in phase I and II of clinical trials for the monoclonal antibody bapineuzumab. These adverse events were subsequently classified as amyloid-related

imaging abnormalities (ARIA), representing a whole spectrum of neuroimaging findings observed in other clinical trials using these antibodies.³ The risk of vasogenic edema and other related extravasated fluid phenomena (ARIA-E) observed in magnetic resonance is increased at higher doses and in apolipoprotein E ϵ 4 allele carriers. There is also little information about the clinical course of patients who present these magnetic resonance imaging findings, most of whom have no or transient mild symptoms. Microbleeding/microhemorrhaging and hemosiderin deposits (ARIA-H) are also related to increased vascular permeability; their relationship with ARIA-H and ARIA-E findings is not yet fully understood.⁴ Bapineuzumab, solanezumab, gantenerumab, and crenezumab had similar outcomes regarding these adverse events (ARIA-E and ARIA-H) and resulted in no improvement in clinical endpoints. They were finally discontinued after futility analysis (Table 1). Initially, aducanumab had the same outcome in the PRIME, ENGAGE, and EMERGE clinical trials. However, further analysis, a longer follow up, a larger sample, and the exclusion of outliers showed that a higher dosage (10 mg/kg) had therapeutic benefits, which led to regulatory filing for Biogen[®]. Initially, the FDA Statistics and Advisory Committees were against approval, although the Office of Neurological Drugs was in favor of it, fast-tracking the drug through the accelerated approval pathway. The agent has shown significantly greater therapeutic benefits than other available treatments, although further study is still required.⁵ Despite aducanumab's approval and benefits, there are many challenges to the development of therapeutic agents for AD. These challenges include anticipating interventions, focusing efforts on preclinical AD, improving methods of subject selection for clinical trials using specific and validated biomarkers, and, finally, the inclusion of other mechanisms of action than the long-established amyloid cascade, considering that multiple pathways may underlie AD's clinical phenotype.

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Table 1 Clinical trials of passive immunotherapeutic anti-amyloid agents and their respective characteristics

Anti-amyloid- β monoclonal antibodies/study	Enrollment	Clinical benefits	Current status
Bapineuzumab Phase III	Probable AD; CDR 1-2	No clinical benefits. ARIA-E (dose- and APOE- ϵ 4 related).	Terminated
Solanezumab Phase III EXPEDITION 1,2 Phase III EXPEDITION 3	Probable AD; CDR 1-2 A β -PET +; CDR 0.5	No clinical benefits (cognition and functional status). No clinical benefits (cognition and functional status).	Terminated Terminated
Gantenerumab Phase III Scarlet RoAD Phase III GRADUATE 1,2	Probable AD; CDR 0.5 A β -PET + or CSF A β ₄₂ + CDR 0.5-1.0	No clinical benefits. ARIA-E (dose- and APOE- ϵ 4 related). Ongoing trial.	Discontinued (futility analysis) Recruiting
Solanezumab and gantenerumab Phase II/III DIAN-TU	ADAD; CDR 0-1	So far, no clinical benefits. Ongoing trial.	Recruiting
Crenezumab Phase II ABBY Phase II BLAZE	Probable AD; CDR 1-2 Probable AD; CDR 1-2	No clinical benefits. No clinical benefits. Safety parameters (ARIA) were met.	Terminated Completed
Phase III CREAD I and II Phase II API-ADAD	A β -PET +; CDR 0.5 PSEN 1 E280A mutation +	Analyses indicated that crenezumab was unlikely to meet its primary endpoint. Ongoing trial.	Discontinued (futility analysis) Active, not recruiting
Aducanumab Phase III ENGAGE Phase III EMERGE	A β -PET +; CDR 0.5 A β -PET +; CDR 0.5	No clinical benefits. Clinical improvement trend with higher dosage.	Discontinued (futility analysis) FDA approval for clinical practice.

A β -PET = amyloid- β positron emission tomography; AD = Alzheimer's Disease; ADAD = autosomal-dominant Alzheimer's disease; API-ADAD = Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's disease; APOE = apolipoprotein E; ARIA-E = amyloid related imaging abnormalities-edema; CDR = clinical dementia rating; CSF = cerebrospinal fluid; DIAN-TU = Dominantly Inherited Alzheimer Network Trial Unit; PSEN 1 = presenilin 1.

Disclosure

The authors report no conflicts of interest.

References

- Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2021. *Alzheimers Dement* (NY). 2021;7:e12179.
- van Dyck CH. Anti-amyloid- β monoclonal antibodies for Alzheimer's disease: pitfalls and promise. *Biol Psychiatry*. 2018;83:311-9.
- Penninkilampi R, Brothers HM, Eslick GD. Safety and efficacy of anti-amyloid- β immunotherapy in Alzheimer's disease: a systematic review and meta-analysis. *J Neuroimmune Pharmacol*. 2017;12:194-203.
- Sperling RA, Jack CR Jr, Black SE, Frosch MP, Greenberg SM, Hyman BT, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement*. 2011;7:367-85.
- Kuller LH, Lopez OL. ENGAGE and EMERGE: truth and consequences? *Alzheimers Dement*. 2021;17:692-5.