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EDITORIAL

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 (Aβ) 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 ε4 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-ε4 related).	Terminated
Solanezumab			
Phase III EXPEDITION 1,2	Probable AD; CDR 1-2	No clinical benefits (cognition and functional status).	Terminated
Phase III EXPEDITION 3	Aβ-PET +; CDR 0.5	No clinical benefits (cognition and functional status).	Terminated
Gantenerumab			
Phase III Scarlet RoAD	Probable AD; CDR 0.5	No clinical benefits. ARIA-E (dose- and APOE-ε4 related).	Discontinued (futility analysis)
Phase III GRADUATE 1,2	Aβ-PET + or CSF $A\beta_{42}$ + CDR 0.5-1.0	Ongoing trial.	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	Probable AD; CDR 1-2	No clinical benefits.	Terminated
Phase II BLAZE	Probable AD; CDR 1-2	No clinical benefits. Safety parameters (ARIA) were met.	Completed
Phase III CREAD I and II	Aβ-PET +; CDR 0.5	Analyses indicated that crenezumab was unlikely to meet its primary endpoint.	Discontinued (futility analysis)
Phase II API-ADAD	PSEN 1 E280A mutation +	Ongoing trial.	Active, not recruiting
Aducanumab			
Phase III ENGAGE	Aβ-PET +; CDR 0.5	No clinical benefits.	Discontinued (futility analysis)
Phase III EMERGE	Aβ-PET +; CDR 0.5	Clinical improvement trend with higher dosage.	FDA approval for clinical practice.

Aβ-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.

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