Editorial: Targets for Disease-Modifying Therapies in Alzheimer's Disease, Including Amyloid β and Tau Protein

Dinah V. Parums, MD PhD

Science Editor, Medical Science Monitor, International Scientific Information, Inc., Melville, NY, U.S.A.
e-mail: dinah.v.parums@isi-science.com

Abstract Current treatments for patients with Alzheimer's disease aim to improve behavioral, cognitive, and non-cognitive symptoms. There have been no new drug approvals for preventing or treating Alzheimer's disease for more than two decades. Drug development in Alzheimer's disease aims to identify disease-modifying therapies that will delay or slow the clinical course of this disease. More than 50% of the current Alzheimer's disease drug pipeline now involves immunotherapies or oral small molecule agents. The most promising disease-modifying drug targets are amyloid β and tau protein. In June 2021, aducanumab, a humanized recombinant monoclonal antibody to amyloid β, was the first potential disease-modifying therapy approved by the US Food and Drug Administration (FDA) to treat Alzheimer's disease and mild cognitive impairment. Accelerated approval of aducanumab was based on the results of only one of two phase 3 clinical trials. Several clinical trials of targeted disease-modifying immunotherapies to the tau protein and amyloid β that commenced before the current COVID-19 pandemic have been delayed. This Editorial aims to provide an update on past, present, and future disease-modifying therapies in Alzheimer's disease, including targeted therapies for amyloid β and tau protein.

Keywords: Editorial • Alzheimer Disease • Amyloid beta-Peptides • tau Proteins • Immunotherapy • Clinical Trial

Alzheimer's disease has distinct neurodegenerative and neuropathological characteristics [1,2]. In the most common form, late-onset Alzheimer's disease, extracellular amyloid deposits begin to occur in the brain and as intracellular neurofibrillary tangles begin up to 20 years before the onset of symptoms [3,4]. Population data from the US, published in 2021, have shown 6.2 million people over 65 years of age currently have Alzheimer's disease, which is the sixth most common cause of mortality in the population and the fifth most common cause of mortality in people over 65 years of age [5]. This number is estimated to increase to 13.8 million by 2060 [5]. In 2021, the annual cost of health care for Alzheimer's disease was $355 billion, possibly exacerbated by the COVID-19 pandemic and the lack of social care provision [5]. The number of patients is expected to double every 20 years, with a projected total annual cost that will exceed $1 trillion by 2050 [4,5].

Current treatments for patients with Alzheimer's disease aim to improve behavioral, cognitive, and non-cognitive symptoms [6]. The acetylcholinesterase (AChE) inhibitors, rivastigmine, donepezil, and galantamine, and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, have been the main pharmacological treatments for Alzheimer's disease [7,8]. There have been no new drug approvals for preventing or treating Alzheimer's disease for more than two decades [9]. There is

an urgent need to develop treatments that prevent or delay disease onset, slow disease progression, or reduce the symptoms of Alzheimer's disease. Therefore, drug development in Alzheimer's disease is increasingly aimed at disease-modifying therapies that will delay or slow the clinical course of this disease [9]. More than 50% of the current Alzheimer's disease drug pipeline now involves immunotherapies or oral small molecule agents [9]. Potential targets for drug development of disease-modifying therapies in Alzheimer's disease include the production of clearance of amyloid β, the prevention of the development of neurofibrillary tangles by the tau protein, or prevention of cell oxidation and changes in neuronal metabolism associated with Alzheimer's disease [9]. The most promising disease-modifying drug targets are amyloid β and tau.

Basic research, preclinical studies, and clinical studies have highlighted the importance of amyloid β in the pathogenesis of Alzheimer's disease [10]. However, therapeutic targeting of amyloid β has not shown convincing efficacy in phase 3 clinical trials [11]. The lack of progress in drug development may be due to poor trial design, the risk of adverse events, and the lack of clarity regarding monitoring of cognitive function on follow-up. In patients with cognitive impairment, cerebral amyloid β is detected by positron emission tomography (PET) scan or lumbar puncture [12].

Aducanumab is a humanized recombinant monoclonal antibody to amyloid β [10]. The results from a preclinical study in a transgenic mouse model of Alzheimer's disease showed that aducanumab could enter the brain and bind to parenchymal amyloid β [10]. In this mouse model, aducanumab reduced soluble and insoluble brain amyloid β in a dose-dependent manner [10]. In a dose-escalation trial of aducanumab in 165 patients with mild Alzheimer's disease, one year of monthly intravenous infusion of aducanumab reduced brain amyloid β levels in a dose-dependent and time-dependent manner (NCT01677572) [10]. Also, aducanumab variably reduced clinical decline when measured using a Clinical Dementia Rating scale and Mini-Mental State Examination (MMSE) scores [10]. At 12-month follow-up, almost half the patients with mild Alzheimer's disease no longer had cerebral amyloid on PET imaging [10].

In June 2021, aducanumab became the first potential disease-modifying therapy approved by the US Food and Drug Administration (FDA) to treat Alzheimer's disease and mild cognitive impairment [13]. Accelerated approval was given based on the results of only one of two phase 3 clinical trials [14,15]. The two trials were: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects With Early Alzheimer's Disease (EMERGE) (NCT02484547); and A221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (ENGAGE) (NCT02477800). The findings from these trials have undergone review with critical reviews of the results for both efficacy and safety [11,15].

The EMERGE and ENGAGE trials were terminated early and underwent post hoc analysis of additional trial data, which showed reduced brain amyloid β levels on PET imaging [10,16]. In the EMERGE trial, which included 1,638 patients, high-dose aducanumab did not show a clear improvement in cognitive function [16]. In the ENGAGE trial, which included 1,647 patients, there was no significant difference in outcome between the treatment and placebo groups [17,18]. In 40% of patients treated with high-dose aducanumab, side effects included amyloid-related imaging abnormalities (ARIA), edema (ARIA-E) or microhemorrhage (ARIA-H) [17,18]. Although most patients with ARIA were asymptomatic, confusion, visual disturbance, and headache were reported [17,18]. Brain magnetic resonance imaging (MRI) in patients treated with high-dose aducanumab showed fluid-attenuated inversion recovery (FLAIR) hyperintensity with or without microhemorrhages [17,18]. Hypersensitivity, including angioedema and urticaria, was reported in one patient in these clinical trials [17,18].

Although the efficacy of aducanumab has been demonstrated in at least one clinical trial, a reduction in brain amyloid β levels and benefits in clinical endpoints have been inconsistent [10,15]. Post-approval trials are awaited to support any clinical benefit and determine which patients may benefit, other than patients with mild cognitive impairment [16,18]. Also, there are concerns with the use of aducanumab, which include the high costs of this therapeutic monoclonal antibody and the cost of PET scans required for patient selection [18]. This drug requires intravenous use and dosing schedules [18]. Monitoring is required for treatment-related adverse events, including headache, visual disturbances, confusion, and focal neurological signs that need investigation with brain magnetic resonance imaging (MRI) [18].

Because the efficacy of aducanumab in the treatment of Alzheimer's disease remains unclear, there is increasing interest in the development of therapies that target the tau protein in Alzheimer's disease [19,20]. Levels of tau protein and the distribution patterns in the brain on tau-PET imaging are more strongly associated with the severity of the cognitive decline in Alzheimer's disease than amyloid β [19]. Also, it is possible that brain imaging with tau-PET may be used to stage Alzheimer's disease or predict cognitive decline [19,20].

Leuco-methylthioninium (LMTX) is a pro-drug of methylene blue and a second-generation tau aggregation inhibitor (TAI) and the only tau-specific agent to undergo phase 3 clinical trials (NCT03446001). In 2016, two phase 3 clinical trials of LMTX for mild to moderate Alzheimer's disease were completed (TRX-005 and TRX-015) [21]. These studies compared LMTX doses of 150-250 mg/day. In the TRX-015 trial, 8 mg/day showed the same benefit as the higher doses [21]. LMTX monotherapy was more effective than co-administration with cholinesterase inhibitors or memantine [21]. A third phase 3 clinical trial, LUCIDITY, is in progress to evaluate the efficacy of low-dose monotherapy, with results expected in late 2021 (NCT03446001). Adverse events with LMTX included dysuria, diarrhea, and anemia, but no cases of ARIA have been reported (NCT03446001). In 2018, the FDA granted LMTX orphan drug designation for the treatment of frontotemporal dementia [21].

In the past decade, there have been increasing numbers of investigational studies of targeted immunotherapy to the tau protein [9]. Several therapeutic anti-tau monoclonal antibodies have been evaluated in phase 2 clinical trials, and one tau vaccine, AADvac1, has been evaluated in phase 2 clinical trials [9]. ABBV-8E12 (or C2N8E12) is an IgG4 antibody that targets aggregated tau protein [22]. Preclinical and phase 1 clinical trial data evaluated the safety and dosing of ABBV-8E12 as a single dose in patients with progressive supranuclear palsy (PSP) [22]. The results showed that ABBV-8E12 was safe and was a potential treatment for Alzheimer's disease [22]. A 96-week phase 2 safety and efficacy trial includes 453 study participants aged 55-85 years with Alzheimer's disease (NCT02880956).

Gosuranemab (BIIB092) is a therapeutic monoclonal antibody to the N-terminal of extracellular tau. A single ascending dose

study showed that the intravenous formulation of gosuranemab (BIIB092) was safe and well-tolerated and resulted in a 12-week persistent suppression of unbound N-terminal tau [23]. Gosuranemab is currently undergoing a phase 2 trial with 654 participants with mild cognitive impairment or mild Alzheimer's disease with different intravenous doses once every four weeks or once every 12 weeks (NCT03352557).

Semorinemab (RO7105705, MTAU9937A, RG6100) is a therapeutic antibody that also targets the N-terminus of extracellular tau and recognizes six isoforms [24]. A pilot study of safety and tolerability and dosing of semorinemab showed promising results, with a further trial of semorinemab including 260 patients with moderate Alzheimer's disease (NCT03828747) [24].

Zagotenemab (LY33003560) is a monoclonal antibody that binds to tau aggregates by recognizing a conformational epitope in the N-terminus of tau [25]. Early phase trials of zagotenemab were conducted in patients with mild cognitive impairment or mild Alzheimer's disease receiving a single dose (NCT02754830) or repeat doses of zagotenemab (NCT030019536) [25].

One tau vaccine, AADvac1, has been evaluated in phase 2 clinical trials. AADvac1 contains fragment 294-305 of the tau protein, coupled to keyhole limpet hemocyanin (KLH) [26]. The initial phase 1 safety and efficacy trials of AADvac1 showed favorable safety, with 29 out of 30 patients developing an IgG immune response (NCT01850238 and NCT02031198) [26]. A 24-month phase 2 trial will be evaluating the safety and efficacy of AADvac1 in patients with mild Alzheimer's disease (NCT02579252).

Preclinical and clinical studies that support future disease-modifying tau-targeted immunotherapy in Alzheimer's disease have begun to show promise during the past decade [27]. There are also potential targets for disease-modifying therapeutic targets other than amyloid β and tau for Alzheimer's disease [9,28]. The Common Alzheimer's and Related Dementias Research Ontology (CADRO) has identified early-stage and late-stage clinical drug development targets [28,29]. Additional potential targets include apolipoprotein E (apo-E), lipoprotein receptors, neurogenesis factors, neurotransmitter receptors, inflammatory mediators, oxidative stress factors, angiogenesis and growth factors, and apoptotic factors [28,29]. The advantage of having a program such as CADRO to systematize the processes in Alzheimer's disease is to provide a classification framework for drug targets and the mechanism of potential disease-modifying therapies [28,29]. Because there have been so many failed phase 3 trials that included patients with symptomatic Alzheimer's disease, trials of disease-modifying therapies should be conducted much earlier, either during the preclinical or mild cognitive impairment phase of Alzheimer's disease [30]. In 2018, the FDA published draft guidance for drug development in early Alzheimer's disease that supports three stages leading to early Alzheimer's disease [30]. The FDA also recommends using the term 'persistent effect' on disease course instead of a 'disease-modifying effect [31].

Conclusions

In the past decade, there has been an increased understanding of potential targets for disease-modifying therapies that will delay or slow the clinical course of Alzheimer's disease, in addition to amyloid β and tau protein. Despite the controversy associated with the recent accelerated approval of aducanumab and the effects of the COVID-19 pandemic on the progress of clinical trials, the range of potential disease-modifying therapies in Alzheimer's disease may lead to future further approvals.

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