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REVIEW ARTICLE

Anti-amyloid antibody treatments for Alzheimer's disease

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Abstract

Our aim is to review the most recent evidence on novel antibody therapies for Alzheimer's disease directed against amyloid-β. This is a joint statement of the European Association of Neurology and the European Psychiatric Association. After numerous unsuccessful endeavors to create a disease-modifying therapy for Alzheimer's disease, substantial and consistent evidence supporting the clinical effectiveness of monoclonal antibodies aimed at amyloid-β is finally emerging. The latest trials not only achieved their primary objective of slowing the progression of the disease over several months but also demonstrated positive secondary clinical outcomes and a decrease in amyloid-β levels as observed through positron emission tomography scans. Taken as a whole, these findings mark a significant breakthrough by substantiating that reducing amyloid-β yields tangible clinical benefits, beyond mere changes in biomarkers. Concurrently, the regular utilization of the new generation of drugs will determine whether statistical efficacy translates into clinically meaningful improvements. This may well signify the dawning of a new era in the development of drugs for Alzheimer's disease.

KEYWORDS
anti-amyloid immunisation, fluid and imaging biomarkers, mild cognitive impairment and dementia, monoclonal antibodies, treatment of cognitive decline

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by the progressive decline of cognitive and functional abilities. It is the most common form of dementia, accounting for up to 70% of all cases. The prevalence of AD increases with age, affecting approximately 10% of individuals over 65 years of age and up to 50% of individuals over 85 years of age.

In addition to the impact on the individual, AD has a significant economic burden on society, with estimated annual costs of $305 billion in the United States alone [1].

The underlying pathology of AD is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein in the brain. These pathological hallmarks disrupt normal neuronal communication and ultimately lead to neuronal death and cognitive decline [2]. Until recently, there were no disease-modifying therapies for AD. However, several anti-Aβ monoclonal antibody treatments have been developed in recent years, targeting the accumulation of Aβ in the brain. Here, the expected effects of these new antibody treatments for AD, including their potential impact on disease progression, current biomarkers for diagnosis and future developments in the field, are discussed.

AMYLOID-β AS A TREATMENT TARGET AND CURRENT BIOMARKERS OF ALZHEIMER'S DISEASE

The accumulation of Aβ plaques in the brain is thought to be an early event in the pathogenesis of AD, followed by the hyperphosphorylation of tau protein. These pathological hallmarks lead to neuronal dysfunction, inflammation and ultimately neuronal death [2]. Whilst these core pathological features of AD are well established, their exact role in disease progression is still under investigation. It is unclear whether the accumulation of Aβ plaques and tau protein is a cause or consequence of the disease. Nevertheless, targeting the accumulation of Aβ in the brain is currently the most prevalent approach to AD disease-modifying treatments.

Diagnosing AD can be challenging, as the symptoms of the disease are similar to those of other forms of dementia and very early clinical signs overlap with physiological cognitive changes due to older age. Traditionally, the diagnosis of AD was based on clinical criteria, including a progressive amnestic syndrome and impairment of normal daily activities [3]. However, the accuracy of clinical diagnoses is limited, with at least 20% of patients diagnosed with AD based on clinical criteria having no underlying AD pathology. Biomarkers for AD have been developed to aid in diagnosis and monitor disease progression. Currently available biomarkers are cerebrospinal fluid Aβ and tau protein levels, as well as Aβ and tau positron emission tomography (PET) imaging. These biomarkers have shown promise in identifying individuals with underlying AD pathology, including in early stages of the disease [4]. However, these biomarkers are invasive and difficult to scale.

BLOOD-BASED BIOMARKERS

Early detection and accurate diagnosis of AD are critical for providing effective treatment and care for patients. Blood-based biomarkers (BBBMs) have emerged as promising tools for diagnosing and monitoring AD progression. The most extensively studied BBBMs for AD are Aβ peptides, tau proteins and neurofilament light chain (NfL). Several studies have demonstrated that plasma and serum levels of Aβ42 and the ratio of Aβ42/Aβ40 are reduced in patients with AD, indicating that these BBBMs may be useful for detecting early stages of AD [5]. However, the diagnostic accuracy of Aβ peptides is limited, as they may also be reduced in other neurodegenerative disorders such as Lewy body disease [6].

Tau proteins are intracellular proteins that play a crucial role in stabilizing microtubules in neurons. In AD, tau proteins become hyperphosphorylated and aggregate to form neurofibrillary tangles, leading to neuronal dysfunction and cell death. Several studies have shown that plasma and serum levels of tau proteins, particularly phosphorylated tau, are elevated in AD patients compared to healthy controls [7]. Similar to Aβ peptides, tau proteins may also be elevated in other neurodegenerative disorders, including Lewy body disease [8]; still, phosphorylated tau is currently the most promising BBBM candidate for routine use in AD diagnosis and as a surrogate biomarker in clinical trials [9].

Neurofilament light chain is a cytoskeletal protein that is released into the cerebrospinal fluid and blood following neuronal damage. Several studies have demonstrated that plasma and serum levels of NfL are elevated in patients with AD and other neurodegenerative disorders, reflecting the degree of neurodegeneration and predicting disease progression [10]. NfL may also be useful for monitoring the response to treatment in clinical trials [9]. However, NfL levels may also be elevated in other conditions, such as frontotemporal dementia, which may limit its specificity for AD [11].

One advantage of BBBMs is their non-invasive and cost-effective nature, making them ideal for large-scale case finding and monitoring. BBBMs also have the potential to complement existing imaging-based biomarkers, such as PET and magnetic resonance imaging, which are more expensive and less accessible. Whilst BBBMs have shown promising results in research settings, there are still several challenges that need to be addressed. For example, there is currently no standardization in the way biomarkers are measured, and different methods may produce inconsistent results. Continued research in this area will probably lead to the routine use of BBBMs for AD diagnosis in the next few years.

ANTI-AMYLOID MONOCLONAL ANTIBODIES

The first anti-Aβ antibody to be studied in phase 3 clinical trials, bapineuzumab, was developed in the early 2000s. It binds to the N-terminus of Aβ and was designed to clear Aβ plaques from the brain. Bapineuzumab showed promise in early clinical trials, but later trials failed to show significant clinical benefits, possibly due to inadequate dosing or patient selection [12]. Solanezumab, another anti-Aβ antibody no longer in active development, targets the mid-region of Aβ and was developed with the goal of preventing Aβ aggregation.

Clinical trials of solanezumab have yielded mixed results, with some studies showing a slowing of cognitive decline in mild AD patients whilst others did not show significant benefits [13].

Aducanumab is an anti-Aβ antibody that targets aggregated forms of Aβ, specifically the Aβ fibrils that make up Aβ plaques. In phase 1b and 2 clinical trials, aducanumab reduced Aβ plaques in the brain and showed a dose-dependent effect on slowing cognitive decline in patients with early AD [14]. Based on these results, Biogen initiated two phase 3 clinical trials of aducanumab, which were later discontinued based on a pre-planned futility analysis. However, after a reanalysis of the phase 3 data, accelerated approval in the United States was granted by the Food and Drug Administration (FDA) in June 2021 based on the positive biomarker results but with residual uncertainty about the clinical benefits [15]. Whilst biomarker evidence was sufficient for approval by the FDA, the European Medicines Agency was unlikely to follow the US decision and the developer therefore withdrew the marketing authorization application; approval for the marketing of aducanumab will not be granted in the EU [16].

Lecanemab (BAN2401) is the humanized version of murine mAb158, raised against Aβ protofibrils, regarded by some researchers as particularly important for driving downstream pathological changes [17, 18]. In September 2022, positive top-line results of the CLARITY-AD phase 3 study were announced, indicating that lecanemab had reached its primary end-point of reducing clinical disease progression on the clinical dementia rating sum-of-the-boxes (CDR-SB) [19]. All clinical and biomarker secondary end-points were also met; importantly, lecanemab showed superior efficacy on measures of quality of life and caregiver burden compared to placebo. Over the 18-month study period, both treatment and placebo groups had deteriorated on the CDR-SB as expected in a chronic progressive disease; however, deterioration in the lecanemab group was 27% slower compared to placebo, resulting in a statistically highly significant difference ($p < 0.0001$) [20]. Three deaths from brain hemorrhage have been reported in the lecanemab open-label extension [21]. Two of the three people had received blood thinners. In the CLARITY-AD phase 3 study, macrohemorrhages, defined as any brain bleed larger than 1 cm, occurred in 0.6% in the treatment group and 0.1% in the placebo group. For people on anticoagulants and lecanemab, the rate increased to 2.4%. Careful patient selection and treatment monitoring will therefore be required to ensure patient safety and maximize treatment benefits. In January 2023, the FDA approved lecanemab under the accelerated approval pathway, based on evidence of effect on the surrogate end-point of Aβ removal in the phase 2 trial and a reasonable likelihood of clinical benefit [22]. Decisions on traditional approval in the United States and approvals in other regions, including the EU, are expected in the upcoming months. On 9 June 2023 an advisory panel of the FDA voted unanimously that lecanemab shows clinical benefit for the treatment of early AD, paving the way for full approval.

Another promising anti-Aβ antibody in development was gantenerumab. Gantenerumab targets aggregated forms of Aβ, similar to aducanumab, but binds to a different part of the Aβ protein. In the initial phase 3 clinical trial, gantenerumab failed to show significant benefits in patients with early AD. However, a subset analysis suggested that patients with milder forms of AD may have benefited from the drug [23]. Therefore, Roche decided to conduct two new phase 3 clinical trials using higher doses of gantenerumab. In November 2022, the results of the GRADUATE 1 and 2 trials were announced, indicating that gantenerumab failed to meet the primary end-point, and no further studies are planned [24].

Several other anti-Aβ antibodies are currently in development for AD. One of these is donanemab, which targets a specific conformation of Aβ that is present in the earliest stages of plaque formation, before plaques become visible on brain imaging. In a phase 2 clinical trial, donanemab reduced Aβ plaques in the brain and showed a statistically significant slowing of cognitive decline in patients with early AD [25]. On 3 May 2023 the top-line results of the phase 3 trial were announced in a press release, stating that donanemab treatment versus placebo slowed clinical deterioration by 35% and a decline of activities of daily living by 40%. All secondary end-points were also met. Full results have also been published since then, indicating that donanemab significantly slowed clinical progression at 76 weeks in those with low/medium tau load on PET and in the combined low/medium and high tau pathology population [26]. These findings suggest that treatment effects may be greatest in the earliest disease stage. The targeting of different Aβ aggregation states by different antibodies is illustrated in Figure 1.

OUTLOOK FOR THE ALZHEIMER'S DISEASE THERAPY FIELD

The development of anti-Aβ monoclonal antibodies represents a significant advance in the treatment of AD. However, many challenges remain in the search for effective therapies for this devastating condition. One of the most pressing issues is the need for more accurate and reliable biomarkers to diagnose AD and track disease progression. Whilst advances have been made in this area, much work remains to be done to identify biomarkers that are sensitive, specific and can easily be measured in clinical practice. New biomarkers are also required that are able to indicate sufficient treatment response, enabling reliable decisions to stop or pause treatment, benefiting patients and payors. Another area of active research is the development of combination therapies that target multiple pathological pathways implicated in AD. For example, researchers are investigating the use agents that target tau pathology, neuroinflammation and synaptic dysfunction [27]. Preliminary results from some of these studies are promising, and it is possible that combination therapies may ultimately prove more effective than single-agent therapies.

In addition to these efforts, there is growing interest in the use of non-pharmacological interventions to manage AD. These include interventions such as cognitive training, physical exercise and nutritional interventions that may improve function and reduce the risk of cognitive decline in older adults [28]. Whilst these interventions may not be as powerful as pharmacological therapies, they have the advantage of being low-cost and accessible to a wide range of patients.

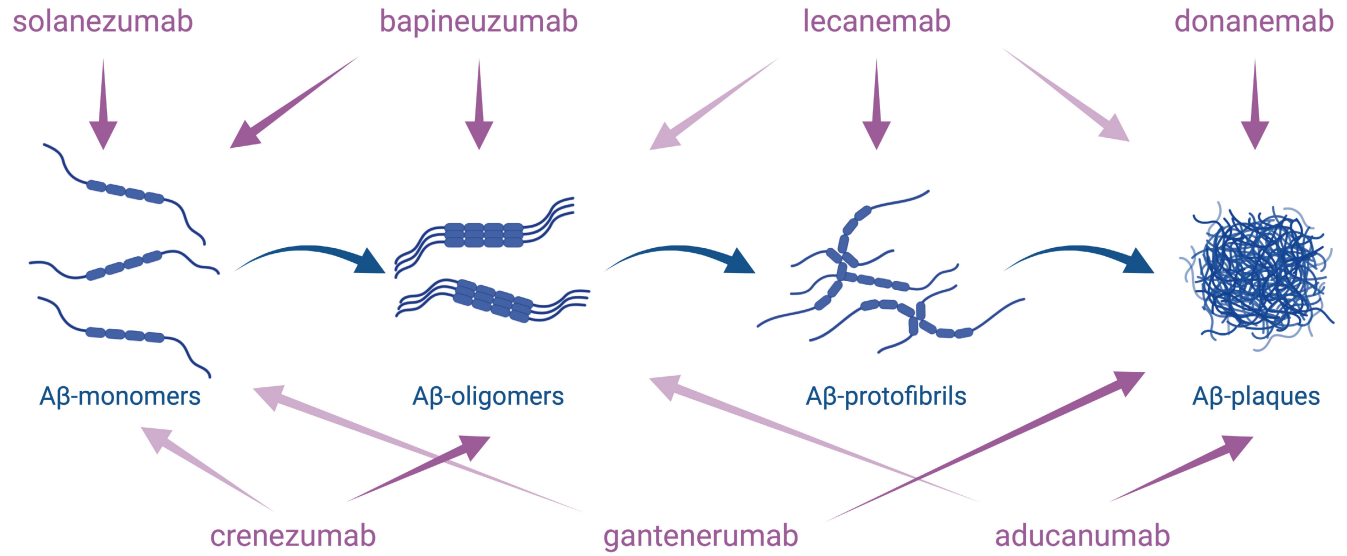

FIGURE 1 Schematic illustration of various antibodies targeting different amyloid-β aggregation states (Source: developer data; reprinted with permission from reference 29).

Anti-Aβ antibodies represent a significant advance in the treatment of AD, but their effectiveness is moderate and much work remains to be done to improve their efficacy, safety and accessibility. It is important to note that anti-Aβ antibodies have not been shown to reverse cognitive decline or halt the progression of AD. Rather, their primary benefit is in slowing the rate of decline in cognitive and daily function. As such, these treatments should be considered as part of a comprehensive approach to managing AD that includes lifestyle modifications, supportive care and other pharmacological interventions as appropriate. Nonetheless, the development of these therapies represents an important step forward in the fight against this devastating condition, and provides hope for a brighter future for patients and their families.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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