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Recent Advances in Alzheimer's Disease Treatments with Therapeutic Antibodies to Amyloid-β

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ABSTRACT

Alzheimer's disease (AD) is one of the most prevalent and devastating neurodegenerative disorders which affects tens of millions of patients. It imposes significant physical, emotional, and financial burdens on patients, families, and society. Formation of Amyloid-β (Aβ) plaques from the accumulation of Aβ peptides in the cortex and hippocampal region is considered one of the fundamental neuropathological pillars of the disease. Pathological Aβ peptides are generated from its precursor protein through proteolysis. Four small molecule medications were approved by the U. S. Food and Drug Administration (FDA) since 1968 to treat the cognitive symptoms of AD, but they are not curative and have no effect on the development of AD. At least four anti-Aβ antibodies and dozens of other anti-Aβ small molecule agents have been evaluated in clinical trials in the past decades but none of them showed consistent clinical efficacy, presumably because they cannot remove Aβ plaques effectively enough or other reasons such as the patient selection and trial design. Despite the failures, more anti-Aβ antibodies are under development, aiming for more efficient Aβ plaques removal through selectively targeting Aβ oligomers. Among those aducanumab was approved by FDA in 2021 as the first drug to address the underlying biology of AD rather than the symptoms.

Introduction

Alzheimer's disease (AD) is defined as a progressive degenerative brain disorder that slowly destroys memory and thinking skills, and eventually the ability to carry out the simplest tasks. It is the most prevalent form of dementia, accounting for 60–80% of cases (Sengupta, Nilson, & Kayed, 2016). Dementia is a general term for memory loss and other cognitive abilities serious enough to interfere with daily life. It is characterized by a decline in thinking and independence in personal daily activities. AD is one of the most widespread and devastating neurodegenerative disorders (Jeremic, Jimenez-Diaz, & Navarro-Lopez, 2021).

AD is a chronic disease, where dementia symptoms gradually worsen over time. The majority of patients with AD are 65 and older but AD is not a normal part of aging. On average, a patient with AD lives 4 to 8 years after diagnosis but can live 20 years or longer with the diagnosis in some cases, depending on the progress of the disease. AD may also affect a person under 65 which is referred to as early-onset AD or younger-onset AD (Alzheimer's Association, 2022).

AD is an irreversible disease leading to gradual deterioration of neurons mainly in the cortex and hippocampal region of the brain which clinically highlights the loss of memory and cognitive dysfunction (Kwak, Lee, Yang, & Park, 2018). This deterioration is due to synaptic failure and specifically in AD is highlighted by excess aggregation of misfolded proteins (amyloid plaques and neurofibrillary tangles) (Salwa & Kumar, 2021), Although the clinical evolution and the form of the symptoms can vary, AD usually starts as

short-term memory loss, followed by later alteration in language and in visuospatial and executive functions. AD changes typically begin in the parts of the brain that affect learning. Microscopic changes in the brain occur long before the first onset of symptoms and thus long before the diagnosis. The most common early symptom of AD is difficulty remembering newly learned information and early stages of symptomatic AD affect primarily cognitive function. What begins as subtle difficulty learning and recalling new information, insidiously progresses to episodes of disorientation and confusion. As AD advances through other region of the brain, it leads to more severe symptoms, including disorientation; mood and behavior changes; deepening confusion about events, time, and place; delusional paranoia; more serious memory loss and behavior changes; and difficulty speaking, swallowing, and walking (Haddad et al., 2022). The duration of each stage and rate of progression varies and is influenced by factors such as age, genetics, and predisposing conditions (Alzheimer's Association, 2022). Progression of AD eventually accelerates the patient's death due to loss of balance and coordination which causes them to fall, erosion of autonomic functions such as heart rate, digestion, breathing, self-feeding, and acquisition of secondary illnesses, most commonly pneumonia (Salwa & Kumar, 2021).

Discovery of AD

AD was first described by a German clinical psychiatrist and neuroanatomist Dr. Alois Alzheimer in 1906. He noticed and reported the presence of amyloid plaques and neurofibrillary tangles, as well as a massive loss of neurons in the cerebral cortex when he carried out a morphological and histopathological examination of the autopsied brain of a presenile dementia patient who suffered from loss of memory and alterations in personality. Since Dr. Alzheimer was the first to link the plaques and tangles to progressive dementia, the disease was named after him by Dr. Emil Kraepelin in 1910 in his 8th edition *Compendium der Psychiatrie* handbook (Breijyeh & Karaman, 2020; Cipriani, Dolciotti, Picchi, & Bonuccelli, 2011; Hippius & Neundörfer, 2022).

Prevalence of AD

AD is the most prevalent neurodegenerative disease in aging. It affects over 44 million patients worldwide but few treatments are currently available (Esmail & Danter, 2021). It also affects the family members of the patients who often take on the role of caregivers. In the US, AD is the most common cause of dementia in the elderly population and one of the leading causes of death. It was reported to consume 8% of the total United States healthcare expenditure, with medical and nursing outlays accounting for an estimated $290 billion (Haddad et al., 2022). According to the Alzheimer's Association, an estimated 6.5 million Americans which are 1 in 9 (10.7%) aged 65 and older have AD (Alzheimer's Association, 2022).

Women appear to be diagnosed with AD more than men; almost two-thirds of Americans diagnosed with AD are women. At age 45, the estimated lifetime risk for AD is 1 in 5 (20%) for women and 1 in 10 (10%) for men; the risk further increases at age 65. Of the 6.5 million people aged 65 and older with AD in the US, 4 million are women and 2.5 million are men. This represents 12% of women and 9% of men aged 65 and older in the US (Rajan et al., 2021). This observed difference was suggested to be likely due to women's average longer lifespan (Haddad et al., 2022).

As for racial and ethnic differences, underrepresented groups appear to demonstrate a higher prevalence of AD in comparison to the white population. A study reported that 18.6% of African Americans and 14% of Hispanics aged 65 and older have AD compared with 10% of Caucasian seniors (Rajan et al., 2021). However, studies assessing health and socioeconomic factors suggest that racial genetic factors do not account for the large differences in prevalence and incidence among racial groups. This suggests healthcare disparities and socioeconomic factors play a stronger role than that ethnicity and race (Alzheimer's Association, 2022; Chin, Negash, & Hamilton, 2011; Haddad et al., 2022).

Risk Factors

Various risk factors have been proven to influence the development of AD, including non-modifiable factors such as age and genetics, and modifiable factors such as education, smoking, diet, staying socially and mentally active (Alzheimer's Association, 2022).

Age

Age is a strong risk factor for the development of AD (Armstrong, 2019; Hersi et al., 2017). One study reported a 19% increase in prevalence in individuals aged 75-84 years. This further increases to 30-35% in those of 85 years and greater (Armstrong, 2019). The percentage of people with AD increases dramatically with age: 5.0% of people age 65 to 74, 13.1% of people age 75 to 84 and 33.2% of people age 85 or older have AD (Alzheimer's Association, 2022). AD was once thought of as an accelerated form of aging. However, it is important to note that AD is not a normal part of aging and older age alone is not sufficient to cause AD (Haddad et al., 2022; Nelson et al., 2011).

Genetics

Genetic predisposition plays important roles in the pathogenesis of both early-onset and late-onset AD. Early-onset AD (<1% of cases) includes individuals under 65 and is associated with mutations in amyloid-β precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes. PS1 gene has been correlated with 80% of early-onset AD compared to 5% associated with PS2gene (Silva et al., 2019). In contrast, polymorphisms of the apolipoprotein-E (APOE) gene have proven to be important in the development of sporadic late-onset AD (Penney, Ralvenius, & Tsai, 2020).

APOE encodes a glycoprotein that is highly expressed in the liver and brain astrocytes and some microglia, and transports cholesterol in the bloodstream. Cholesterol is essential for myelin production and normal brain function. Due to two single nucleotide polymorphisms (SNPs) which cause changes in the coding sequence, APOE gene has three isoforms: APOE-ε2 (Cys112, Cys158), APOE-ε3 (Cys112, Arg158), and APOE-ε4 (Arg112, Arg158) (Jeremic et al., 2021). Everyone inherits one of three forms (alleles) of the APOE gene from each parent, resulting in six possible APOE pairs: ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4. While the ε3 allele is the most common variant, the ε4 allele is a strong risk factor for late-onset AD. The ε4 allele was also associated with vascular damage in the brain, which leads to AD pathogenesis. More than 50% of AD patients have at least one ε4 allele. Conversely, the ε2 allele has a protective role in the progression of disease. Additionally, there are more than 40 genetic variants associated with risk factors that increase the susceptibility to develop the late-onset AD, and some genes are involved in more than one pathology (Haddad et al., 2022; Li, Shue, Zhao, Shinohara, & Bu, 2020; Alberto Serrano-Pozo, Das, & Hyman, 2021).

Modifiable Risk Factors

The modifiable risk factors have also been proven to influence the development and progression of AD. The level of education achieved is an early-life risk factor. Mid to later-life risk factors include diet, hypertension, hyperlipidemia, cerebrovascular disease, diabetes, obesity, traumatic brain injury (TBI), smoking, alcohol abuse, depression, physical activity, and social and cognitive engagement (Horder et al., 2018). Notably, cerebrovascular disease and AD share common risk factors such as hypertension, diabetes, and smoking. Studies have found a twofold increase in the risk of dementia following a stroke independent of cognitive alteration

prior to the incident. A reduction in blood supply to the brain and disruption in the blood-brain barrier may predispose to amyloidogenic processes. Similarly, hypertension increases the risk of AD due to vascular wall damage and disruption of the blood-brain barrier (Delpak & Talebi, 2020; Haddad et al., 2022; Lautenschlager et al., 2008; Livingston et al., 2020; Mayeux & Stern, 2012; Scarmeas et al., 2009; Silva et al., 2019).

AD and Amyloid-β (Aβ)

AD is the result of a very complex neurodegenerative process. The two most widely accepted etiological hypotheses in the scientific community are the hypothesis of the amyloid cascade and that of the phosphorylation of the tau proteins. The molecular basis of AD has always been highly debated, but the accumulation of amyloid-β (Aβ) in senile plaques and the hyperphosphorylation of tau proteins are considered as the fundamental pillars of the disease (Selkoe & Hardy, 2016; Sengupta et al., 2016).

Aβ is generated from its precursor protein APP (amyloid-β precursor protein) through proteolysis. APP is a plasma membrane protein found in different types of neurons and glial cells. APP is encoded by a gene located on chromosome 21. This protein can be cleaved by α-, β-, and γ-secretase in amyloidogenic and non-amyloidogenic pathways (Folch et al., 2018).

Under physiological conditions, APP is cleaved by α-secretase by non-amyloidogenic pathways. The catabolized products are not toxic to neurons or the brain. Under neuropathological conditions, APP is metabolized by amyloidogenic pathway, in which APP is cleaved by β- and γ-secretase leading to the production of Aβ peptides (mainly Aβ40 and Aβ42, with 40 and 42 amino acids, respectively) (Bressler et al., 1996; Ward et al., 2010). Aβ40 is the predominant one. Extracellular accumulations of Aβ40 and Aβ42 lead to the formation of Aβ oligomers, aggregates, fibrils, and subsequently plaque lesions. The Aβ42 peptide is more neurotoxic and more prone to aggregation than Aβ40. Higher concentrations of Aβ42 were found in amyloid plaques of AD patients (Folch et al., 2018; Kinoshita, Whelan, Smith, Berezovska, & Hyman, 2002; Ward et al., 2010).

Early-onset AD is often caused by rare mutations in three genes which lead to Aβ accumulation. These genes encode APP on chromosome 21, and PS1 and PS2, on chromosome 14 and 1, respectively. Some mutations within and very close to the Aβ region of APP cause early-onset AD, while inheritance of a missense mutation that decreases the production of Aβ protects against AD and cognitive impairment related to age. Additionally, individuals with trisomy 21 (Down's syndrome) who have three copies of chromosome 21 harbor 3 copies of APP gene and develop neuropathologically typical AD (Doran et al., 2017; Wiseman et al., 2015). In contrast, late-onset AD probably reflects the cumulative effects of gradual Aβ deposition resulting from various risk factors (Bekris, Yu, Bird, & Tsuang, 2010; Jeremic et al., 2021; Selkoe & Hardy, 2016).

γ-secretase complex composed of presenilin (PS1 or PS2), nicastrin (NCT), anterior pharynx-defective-1 (APH-1) and presenilin enhancer-2 (PEN-2) Its enzymatic activity is located at presenilin 1 (PS1) or presenilin 2 (PS2). Certain mutations in presenilin give rise to early-onset AD, since they favor the production of longer Aβ peptides which are more prone to aggregation and leading to enhanced Aβ deposition (Fernandez, Klutkowski, Freret, & Wolfe, 2014; Wolfe, 2020).

In addition, hyperphosphorylated tau proteins form neurofibrillary tangles intracellularly. The abnormal accumulation of the Aβ peptides and tau proteins not only leads to the formation of plaques and tangles, but also microglia activation and reactive gliosis of astrocytes. All these pathological changes subsequently lead to toxic effects on neurons causing atrophy, neurotransmitter loss, and eventual loss of cognitive function (Cras et al., 1991; DeTure & Dickson, 2019; A. Serrano-Pozo, Frosch, Masliah, & Hyman, 2011; Silva et al., 2019; Spires-Jones & Hyman, 2014).

FDA Approved Medications for AD Treatment

Before the approval of aducanumab (which will be discussed in detail in a subsequent section) by the U. S. Food and Drug Administration (FDA) in June 2021, only four small molecule medications were approved in the past decades to treat the cognitive symptoms of AD, including acetylcholinesterase enzyme inhibitors (rivastigmine, galantamine and donepezil), and N-methyl-D-aspartate (NMDA) receptor antagonist memantine. The cholinesterase inhibitors are usually administered during the first mild or moderate phases of AD. At later and more severe stages of the disease, cholinesterase inhibitors are often combined with memantine. All these medications have been shown to improve the quality of life by temporarily relieving cognitive symptoms, but they are not curative and have no effect on the progression of the disease (Fink et al., 2020; Husna Ibrahim et al., 2020). Undoubtedly, there are substantial unmet medical needs in AD patients for new innovative treatments, which could not only stop but also reverse the progression of the disease.

Development of First Generation Anti-Aβ Antibodies

Antibodies, also known as immunoglobulins, are large, Y-shaped proteins used by the immune system to identify and neutralize foreign objects such as pathogenic bacteria and viruses. Antibodies were also developed as therapeutic agents to treat diseases (Buss, Henderson, McFarlane, Shenton, & de Haan, 2012;). The first FDA approved therapeutic antibody was muromonab, which is a murine monoclonal antibody to human CD3 molecule developed for the treatment of acute transplant rejection (Wilde & Goa, 1996). Due to its murine origin, it induces immune (anti-drug) reactions in human bodies. To avoid these side effects newer generation therapeutic antibodies from non-human species were usually "humanized", which means the sequences of the antibodies are modified to increase their similarity to natural human antibodies (Adair et al., 1994). More than 100 antibody drugs have been approved by FDA and the authorities in other countries for the treatment of various diseases including cancer, inflammatory disease, organ transplantation, cardiovascular disease, respiratory disease, infection, and so on (Singh et al., 2018).

As discussed previously, it has been broadly accepted that misfolding, oligomerization, and progressive accumulation of cerebral deposits of Aβ are a central event in AD (Mucke & Selkoe, 2012; Urayama et al., 2022). Thus, preventing and removing Aβ aggregates is one of the most promising strategies to treat the disease. Various approaches including γ-secretase inhibitors, β-site amyloid precursor protein cleaving enzyme 1 (BACE1, β-secretase) inhibitors, and at least four anti-Aβ antibodies bapineuzumab, crenezumab, ponezumab and solanezumab have been evaluated in clinical trials but none of them has been able to demonstrate clinical efficacy so far (Karran & De Strooper, 2022).

Bapineuzumab

Bapineuzumab was developed by the pharmaceutical companies of Élan and Wyeth. It was the first anti-Aβ antibody tested in a late-phase clinical trial. It is a humanized IgG1 monoclonal antibody against the Aβ N-terminus (AA 1–5) (van Dyck, 2018). It binds to the monomer, oligomer, and fibril forms of Aβ. Although in several clinical trials it demonstrated reduction of fibrillar Aβ accumulation, it failed to improve clinical outcomes in AD patients. Bapineuzumab was also the first antibody to be found to cause the side effects of amyloid-related imaging abnormalities (ARIA) in patients, including accumulation of fluid in brain tissue, which were observed in patients treated with other anti-Aβ antibodies (Ivanoiu et al., 2016; Ketter et al., 2017; Liu et al., 2015; Salloway et al., 2014; Vandenberghe et al., 2016).

Crenezumab

Crenezumab was developed by AC Immune and Genentech. It is a humanized IgG4 monoclonal antibody targeting the mid-region (AA 13–24) of Aβ. Crenezumab is similar to bapineuzumab with respect to the non-selective binding of monomeric, oligomeric, and fibrillar Aβ species (Suzuki, Iwata, & Iwatsubo, 2017). In clinical trials, administration of crenezumab reduced the CSF levels of Aβ oligomers significantly. However, larger trials were discontinued because interim analysis indicated that cognitive decline was unlikely to be slowed, so it was unlikely that this drug would meet its primary endpoint (Kwan, Konno, Chan, & Baum, 2020).

Ponezumab

Ponezumab was developed by Pfizer. It is a humanized IgG2 monoclonal antibody, directed to the C-terminal end of Aβ40 (AA 30–40). It binds to the oligomer and fibril forms of Aβ40 but not to monomer, oligomer, or fibril forms of Aβ42. In clinical trials, ponezumab was safe and well tolerated. However, it didn't change CSF Aβ levels or decline of cognition. Since no clinical benefits were obtained, the trials were discontinued (Cehlar, Skrabana, Revajova, & Novak, 2018; Goure, Krafft, Jerecic, & Hefti, 2014; Kwan et al., 2020; Miyoshi et al., 2013).

Solanezumab

Solanezumab was developed by Eli Lilly. It is a humanized IgG1 monoclonal antibody. It also binds to the mid-region of Aβ (AA 16–26) and targets a similar epitope to crenezumab. It stabilizes Aβ monomers and prevents the formation of Aβ oligomers, but it does not target fibrils. Early clinical studies confirmed its safety and tolerability, including its low incidence of ARIA, but later clinical trials did not achieve adequate cognitive and functional outcomes, although solanezumab was able to reduce the levels of Aβ in CSF significantly, which indicates that reducing Aβ in CSF might not be sufficient to slow down the progress of AD (Honig et al., 2018; Se et al., 2021; Suzuki et al., 2017).

Ineffectiveness of First Generation Anti-Aβ Antibodies

Including the aforementioned four anti-Aβ antibodies, dozens of different anti-Aβ agents have failed in various clinical trials. The failures may be due to the drugs themselves because none of these early agents showed the ability to effectively remove Aβ plaques, and several had deleterious off-target effects. Another reason could be the trial design because these studies enrolled patients without evidence of amyloid pathology and targeted patients with more advanced symptomatic AD, which is perhaps too late for intervention (Musiek & Bennett, 2021).

AD Treatment with More Effective Second Generation Anti-Aβ Antibodies

Despite these previous failures, more anti-Aβ antibodies are under development, especially those ones selectively targeting Aβ oligomers and show high potential to reduce and remove Aβ plaques in patients' brain, since they may be more effective to treat AD than those antibodies targeting monomeric Aβ (Goure et al., 2014; Mantile & Prisco, 2020). Several antibodies including aducanumab, lecanemab, donanemab, and gantenerumab are either under evaluation in late-stage clinical trials or already approved by FDA and have shown promising efficacy (Panza, Lozupone, Logroscino, & Imbimbo, 2019). All of them have shown strong evidence of Aβ removal and demonstrated promising effects of slowing decline in patients with early AD.

Aducanumab

Aducanumab was developed by Biogen and marketed under the brand name Aduhelm. It was controversially approved by the FDA in June 2021 for the treatment of AD. It is the first FDA-approved drug to address the underlying biology of AD rather than the symptoms. Aducanumab is an endogenous human IgG1 monoclonal antibody derived by selecting human B cell clones from healthy elderly people with no signs of cognitive impairment, and cognitively impaired elderly people with unusually slow cognitive decline. The rationale of this strategy was that the immune system of such people successfully suppressed AD and, therefore, the transplantation of their antibodies may exert protective effects in other patients with AD. Aducanumab binds to Aβ42 oligomers with high affinity but does not bind soluble Aβ40. It is specific to the N-terminal residues (AA 3-7) of the Aβ sequence. It selectively reacts with Aβ aggregates, including soluble oligomers and insoluble fibrils rather than monomers. Importantly, it reduces brain Aβ plaques in patients with AD. It also induces microglial activation and phagocytic response, possibly by Fc receptor mediated phagocytosis of antibodies–Aβ complexes (Jeremic et al., 2021; Sevigny et al., 2016).

Aducanumab was evaluated in two large phase 3 clinical trials (EMERGE and ENGAGE) which have identical design and both terminated for futility in August 2020. Further analysis of the data showed that the EMERGE trial met its primary outcome and the ENGAGE trial did not. Nevertheless, FDA granted aducanumab marketing approval using the accelerated approval pathway, which can be used for a drug for a serious or life-threatening illness that provides a meaningful therapeutic advantage over existing treatments. Accelerated approval can be based on the drug's effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients, with a required post-approval trial to verify that the drug provides the expected clinical benefit. The surrogate endpoint used in aducanumab study was significant reduction in Aβ plaques, observed using positron emission tomography (PET) in both trials. However, the link between this biomarker change and cognitive improvement hasn't been validated clinically (Cummings et al., 2021). The approval of aducanumab is one of the most consequential and criticized decisions FDA has made in years which led to many controversies and open questions (Jeremic et al., 2021; Steinbrook, 2021). Biogen was required to conduct a further appropriately controlled phase 4 clinical study to verify the efficacy of aducanumab and submit the final report by February 2030 (Karran & De Strooper, 2022).

Lecanemab

Lecanemab was developed by Eisai and Biogen and received FDA's Breakthrough Therapy designation for treatment of AD in June 2021. FDA has accepted the Biologics License Application (BLA) under the accelerated approval pathway for lecanemab for the treatment of early AD with confirmed presence of amyloid pathology in the brain. Lecanemab is a humanized IgG1 monoclonal antibody and binds to the N-terminal residues (AA 1-16) of the Aβ sequence (Plotkin & Cashman, 2020). It preferentially targets soluble aggregated Aβ, with activity across oligomers, protofibrils, and insoluble fibrils, and allows reduction of amyloid plaques (Jeremic et al., 2021; Swanson et al., 2021). Recent clinical studies showed that lecanemab failed to meet the 12-month primary endpoint. However, results from prespecified key secondary endpoint analyses demonstrated reduction in brain Aβ levels, accompanied by a consistent reduction of clinical decline across several clinical and biomarker endpoints. Larger clinical trials in early AD are underway (Logovinsky et al., 2016; Swanson et al., 2021).

Donanemab

Donanemab was developed by Eli Lilly and received FDA's Breakthrough Therapy designation for treatment of AD in June 2021. It is a humanized IgG1 monoclonal antibody that targets a unique N-terminally truncated 3-x Aβ peptide in which the N-terminal glutamate is cyclized to form the pyroglutamate (pE3Aβ). The pE3Aβ epitope is restricted to the Aβ species which are present exclusively in established plaques. It is specific for this epitope and shows no off-target binding to other Aβ species, therefore donanemab could be considered as plaque-specific (Demattos et al., 2012; Karran & De Strooper, 2022). In an early phase 1b study involving patients with amyloid-positive mild cognitive impairment or mild-to-moderate AD with dementia, donanemab reduced the amyloid plaque level even after a single dose. In a more recent phase 2 study, donanemab resulted in a better composite score for cognition and for the ability to perform activities of daily living than placebo at 76 weeks in patients with early AD, although results for secondary outcomes were mixed. Longer and larger trials are necessary to study the efficacy and safety of donanemab in AD (Fleisher et al., 2006; Mintun et al., 2021).

Gantenerumab

Gantenerumab was developed by Hoffmann-La Roche and received FDA's Breakthrough Therapy designation for treatment of AD in October 2021. It is a human IgG1 monoclonal antibody discovered with phage display technology. It binds to a conformational epitope including the N-terminal (AA 3-12) and central (AA18-27) portions on Aβ fibrils and clears aggregated Aβ fibers. It works by preventing fibril elongation and by removing amyloid plaques through recruiting microglia and activating Fc receptor mediated phagocytosis. It did not alter plasma Aβ suggesting undisturbed systemic clearance of soluble Aβ (Bohrmann et al., 2012). At lower doses it reduced Aβ levels in brains of AD patients but did not significantly slow cognitive decline, therefore, it is now being tested at higher doses in additional clinical trials (Kwan et al., 2020; Ostrowitzki et al., 2017).

Discussion

Alzheimer's disease (AD) is a progressive neurodegenerative disease. It is often characterized by initial memory loss and cognitive impairment that gradually affect behavior, speech, visuospatial orientation and other daily activities of the patient. Progression of AD leads to more severe symptoms and eventually accelerates the patient’s death often within several years after diagnosis. AD is one of the most devastating neurodegenerative diseases which has no cure. When Dr. Alois Alzheimer first reported AD in 1906, he described the amyloid plaques and neurofibrillary tangles in the brain of a dementia patient. Above two core features led to two therapeutic hypotheses for AD treatment: one targeting aberrant accumulation of extracellular Aβ peptides which form the plaques, and the other targeting intracellular hyperphosphorylated tau proteins which form the neurofibrillary tangles.

Multiple risk factors including age, genetics, and other modifiable factors such as education and diet have been identified to be associated with AD. Genetics studies of Aβ related molecules provided substantial evidence supporting the hypothesis that formation of plaques from the accumulation of Aβ oligomers in the brain is fundamental in the development of AD, which are upstream of tau hyperphosphorylation in AD pathogenesis and triggers the conversion of tau from a normal to a toxic state. The amyloid cascade hypothesis remains to be dominant in AD therapeutic development.

Before the approval of aducanumab by FDA in 2021, the efforts on drug development for AD treatment were not very fruitful since all the medications available only relieve some symptoms and haven’t been

demonstrated to delay progressive loss of cognitive or memory function. Even the aducanumab approval was controversial since the relationship between the removal of Aβ plaques and potential consequent clinical benefit remains to be proved clinically. It led to open questions and challenges due to the skepticism in clinical efficacy. The manufacturer of aducanumab was required by FDA to conduct a further clinical study to verify the efficacy of aducanumab and submit the final report.

The mechanism of how the anti-Aβ antibodies clear the plaques in AD brains is not fully elucidated. The antibodies may interfere with amyloid cascade at different steps by targeting monomers, oligomers, fibrils, or plaques respectively. The antibodies may also sequestrate Aβ in peripheral blood by altering its transport and promoting the outflow of Aβ from the brain (Suzuki et al., 2017). The most widely accepted hypothesis is that anti-Aβ antibodies partially penetrate through the blood brain barrier, so that in the brain parenchyma they inhibit the formation of toxic Aβ oligomers, and promote phagocytic clearance of the plaques by the microglia and the Fc receptor mediated clearance (Suzuki et al., 2017). In clinical trials, microglial phagocytosis of plaques has been observed (Jeremic et al., 2021; Mantile & Prisco, 2020).

The approval of aducanumab by FDA also promoted the development of other second generation anti-Aβ antibodies. Right after its approval, three other antibodies received FDA's Breakthrough Therapy designation for treatment of AD in 2021. They provided additional hope for those working toward the goal of providing patients a safe and viable treatment option in the management of AD.

In the past decades, tremendous efforts from both basic research and therapeutic development have been invested on the AD treatment by targeting Aβ. The understanding of AD pathology has been advanced significantly. However, the underlying molecular mechanisms of AD pathogenesis are still under debate. Recently one of the most influential papers on AD studies, which was published in *Nature* in 2006, was suspected to be a fraud. In this paper, the extracellular accumulation of a 56-kDa soluble Aβ assembly, which was termed Aβ*56, was discovered in a mouse model of AD and proposed to impair memory independently of plaques or neuronal loss, and may contribute to cognitive deficits associated with AD (Lesne et al., 2006). However, some other researchers couldn't replicate the results or find Aβ*56 in human fluids or tissues, and instead they found some images in the paper were fabricated. Skepticism on the amyloid cascade hypothesis arose since the paper is one of the most cited studies in the field. Further studies and investigations are needed to address the concerns (Piller, 2022).

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