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Beta-Amyloid Monoclonal Antibodies for Alzheimer's Disease: Development and Challenges

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Abstract. As one of the most common diseases of the elderly, the detection and diagnosis of Alzheimer's disease (AD) remain a challenge at the early stage. As the disease progresses, patients will suffer from memory and cognitive loss, which will impair their ability to live independently. The care required for these patients will be costly and time-consuming, placing a significant burden on both the family and society. At the same time, Alzheimer's disease has a complex pathogenesis and there is still and there is an unmet need for drugs that can reverse the disease. The beta-amyloid (Aβ) proteins produced by improper cleavage of amyloid precursor proteins tend to aggregate into insoluble plaques in the brain. This study reviews the latest progress in the treatment of AD with Aβ monoclonal antibodies (mAbs). In recent years, aducanumab, lecanemab, donenamab have been successively approved. Besides, small molecule drugs also play an important role in AD treatment. Despite the inability to impede the progression of the disease, they are still irreplaceable and effective in relieving symptoms at this stage. In addition, as Aβ deposition begins decades before clinical symptoms appear, advances in diagnostic technology are essential for early intervention. Future research needs to pay more attention to the side effects of this therapy and their solutions.

Keywords: Dementia, Alzheimer’s disease, monoclonal antibodies, neurodegenerative disease.

1. Introduction

Alzheimer's disease (AD) is a well-known neurodegenerative disease with a predominance of elderly patients, main symptoms include memory loss, cognitive impairment and behavioural changes. In 2019, There were over 9 million AD patients in China [1]. The disease not only impairs the physical and mental health of patients but also places a considerable burden on families and society. However, the pathogens of AD are still being researched. There are three main pathological features: beta-amyloid (Aβ) deposition, neurofibrillary tangles (NFTs) and neuronal loss with brain atrophy. The Aβ deposition is generally considered to be produced by the anomalous cleavage of amyloid precursor proteins (APP). Mutations of presenilin-1 (PS1) and presenilin-2 (PS2) in γ-secretase result in a shift of the cleavage site from amino acid 38 to the position of amino acids 40 and 42. Aβ42 monomers tend to form stable oligomers and grow into protofibrils that induce localised inflammation and eventually lead to damage or dysfunction in the central nervous system [2,3]. Furthermore, Aβ42 oligomers would reduce the number of synapses and play a role in oxidative stress in the early AD symptoms [4]. Clinically diagnostically, NFTs generally appear after amyloid deposition, but their interactions remain unclear. Some studies have shown that Aβ oligomers can contribute to the hyperphosphorylation of Tau protein, a microtubule-associated protein which mainly used to maintain the solidness of axonal microtubules [5]. Compared to healthy bodies, Tau protein is significantly elevated in the brains of Alzheimer's patients. Phosphorylated Tau protein forms double-helical fibrils that initially aggregate into insoluble NFTs, leading to impaired neuronal axonal transport and reduced acetylcholine release. Elevated levels of phosphorylation of Tau generally correspond to cognitive decline in patients and can therefore be an important indicator in diagnosis [6].

The cause of AD is complex and the mechanism is still unclear. Existing drugs are mainly used to relieve symptoms. The acetylcholinesterase inhibitor has been demonstrated to improve cognitive

function and memory in patients by upregulating acetylcholine levels in the brain, with donepezil as a representative drug

Memantine is another commonly used Alzheimer's drug that is an N-methyl-D-aspartate (NMDA) receptor antagonist, protecting neurons from overexcitation by partially blocking the NMDA receptor. However, both donepezil and memantine do not directly target the pathogens of AD. The development of Aβ monoclonal antibodies (mAbs) began in the 1990s. Early Aβ mAbs target the removal of deposits in the brain to reduce the inflammatory response and improve cognition. Early Aβ mAbs targeted amyloid plaques or Aβ42 monomers of deposits in the brain, designed to reduce the inflammatory response and improve cognition. In decades the Aβ mAbs failed in phase III clinical trials with insignificant efficacy as well as severe side effects. The serial failures have led researchers to reconsider the Aβ hypothesis to refine new targets for Aβ mAbs [7]. Neurotoxicity studies of soluble Aβ protofibrils have driven advances in the study of Aβ mAbs. In recent years the newly approved Aducanumab and Lecanemab have both been able to target soluble Aβ protofibrils. Of these, Aducanumab is more selective for insoluble plaques, while partially binding to the Aβ protofibrils. Lecanemab, on the other hand, preferentially selects Aβ protofibrils without binding to monomers or amyloid plaques [7].

It appears that existing Aβ mAb analogues are similarly constrained. While they are capable of clearing targeted Aβ deposition, their efficacy is limited in patients with mid- to late-stage AD. In these patients, clearance of deposits has been observed to reduce inflammation, yet it has not been shown to repair damaged nerve cells or elevate levels of cognitively relevant neurotransmitters and, therefore, has not demonstrated significant efficacy in clinical practice. The deposition of Aβ is observed to precede the onset of cognitive impairment by approximately 20 years. However, existing diagnostic techniques like positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis are associated with physical impairs and are not readily accepted by potential patients. This presents a challenge for the pre-emptive treatment of AD. Additionally, Aβ mAbs present lower bioavailability as protein drugs and some enhancement after the decline of the blood-brain barrier function in the mid and late stage, which seems to be contrary to its advantages in the treatment of early AD. Therefore, in combination with more novel detection technologies and with improved dosage forms, Aβ mAbs may be able to play a more important role in the early treatment of AD.

This article will review the development of Aβ mAbs, comparing their strengths and weaknesses with other types of AD drugs, analysing where they are improving and how the latest diagnostic technologies will affect the future of Aβ mAbs.

2. The Pathogenesis of AD and Its Hypotheses

2.1. Pathogenesis of AD

AD is known as a progressive neurodegenerative disease with symptoms including memory loss, cognitive impairment and behavioural changes. There are over 50 million people with dementia globally, most of them suffering from AD [8]. In recent years, it has not only become one of the most lethal diseases but also places a significant burden on families and society. AD was initially described by Alois Alzheimer in 1907. Subsequent researchers have been dedicated to exploring the pathogens of AD, yet the mechanisms by which this disease develops are still under investigation. Currently, the beta-amyloid deposition and NFTs of tau protein are the mainstream pathognomonic factors that have been widely accepted and supported by numerous experiments [5][9]. The initial observation of fibrous aggregations in the brains of patients with AD marked the beginning of the study. In later research, these abnormal depositions were defined as amyloid plaques and NFTs.

2.2. The Pathology of Aβ

The amyloid Aβ was identified as the main component of amyloid plaques in 1984, in followed years, the discovery of the APP gene locus provided an explanation for the origin of Aβ, and the APP

missense mutation that correlates with inherited AD had further consolidated the Aβ hypothesis [10]. Furthermore, the mutations in presenilin proteins also contribute to the amyloid plaque formation. PS1 or PS2 are in the core of intramembrane gamma-secretase which is responsible for the cleavage of APP. Certain mutations of them would lead to a shift of the cleavage site from amino acid 38 to the position of amino acids 40 and 42 [2]. Aβ42 is produced at higher levels than Aβ40 and forms the stable trimeric or tetrameric oligomers, leading to metabolic imbalance and, therefore, aggregated and eventually deposited around the nerve cells as amyloid plaques [3]. Aβ 42 protofibrils tend to induce localised inflammation, which in turn results in the loss of synaptic spines, and triggers damage or dysfunction in the nervous system. This ultimately leads to neuronal cell death through a cascade of reactions [2]. The transgenic mice experiments have confirmed that Aβ42 fibrils can induce specific tau NFTs and lead to another dementia disease, parkinsonism-17, revealing its upstream effect on tau hyperphosphorylation [11].

2.3. The Pathology of Tau

The tau protein was first discovered as MT-associated proteins (MAPs), which contribute to the self-assembly of axonal microtubules (MTs) of neurons. Tau protein undergoes multiple post-translational modifications (PTMs), since the relationship of soluble Aβ and NFTs began to be investigated, the hyperphosphorylation of tau was considered to be the main component of NFTs [11]. In AD patients the hyperphosphorylated tau forms paired helical filaments and aggregates in the axonal to form the NFTs, which lose the function of associated and stabilised microtubules, thereby leading to neuronal dysfunction [12]. Several kinases are involved in the modification of tau hyperphosphorylation. Glycogen synthase kinase-3 beta (GSK3β) regulates multiple physiological functions in the central nervous system (CNS) and can play an important role in many dementia diseases. The inhibition of GSK3β lowers the phosphorylation level of tau protein and reduces the formation of NFTs [13]. While the presence of Aβ oligomers can upgrade the activation of GSK3β, demonstrated its driving effect with tau protein phosphorylation (p-tau) and the accumulation of NFTs [14]. In contrast to Aβ, the degree of tau phosphorylation is correlated with the progression of AD and is particularly relevant to the patient's level of cognitive ability. Consequently, it can be used as a biomarker and detected in the (CSF). The combination of the p-tau ratio with Aβ indicators is an effective method for determining the stage of AD [11]. It was observed that NFTs induced the inflammation of microglial cells through the TLR2/MyD88 pathway [15]. TLR2 belongs to Toll-like receptors (TLRs), responsible for the recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Myeloid differentiation factor 88 (MyD88) connects the proteins that receive extracellular signals and relay intracellular signals, functions in conjunction with TLRs to activate immune cells.

3. Aβ mAbs Based on the Aβ Hypothesis

The research on mAb classes of drugs targeting Aβ commenced in the 1990s. These pharmaceutical agents are founded upon the amyloid hypothesis and are designed to eliminate Aβ amyloid deposits from the brain. Bapineuzumab was one of the first Aβ mAb drugs to begin development, targeting mature amyloid deposits. Despite its efficacy in reducing amyloid plaque deposition in the brain, the drug did not receive FDA approval due to the insignificant cognitive function improvement in clinical trials [16].

Aducanumab is the first Aβ mAb drug approved by the FDA that primarily targets amyloid plaques and also has the capacity to bind to Aβ oligomers. Aducanumab activates microglia and removes amyloid plaques through an immune response, thereby reducing the neuroinflammatory response caused by the deposits. The approval of aducanumab in 2021 has given rise to some controversy in the academic and medical community. This is largely due to differences in the results of the EMERGE and ENGAGE trials in the Phase III clinical stage [17]. In the meantime, lecanemab takes soluble Aβ oligomers as its primary target. It achieved better results in the CLARITY AD trial and the EMERGE trial and is considered to have the potential to control early Alzheimer's disease [18].

MAbs generally comprise four polypeptide chains, with the two light chains attached to the heavy chains by disulfide bonds to form a Y-shaped structure. The N-terminal end is called the fragment antigen-binding (Fab)region, which is responsible for recognising and binding with the antigen. The C-terminal end is called the Fragment crystallizable (Fc) region, which is responsible for binding to immune cells and triggering the immune effect function. Microglia is the main immune cell that is activated by mAbs and triggers a series of immune responses in the CNS, removing mAbs- Aβ complexes via antibody-dependent cellular phagocytosis (ADCP). Phagocytosis is one of the most important immune functions of microglia, which recognises and removes pathological proteins as well as necrotic or unwanted synapses, maintaining the health of the CNS.

3.1. Biomarker of Soluble Aβ and the Development of Lecanemab

PET as a medical imaging technology, has been used in the diagnosis and disease investigation for a long time. It has become a well-established method for diagnosing AD, enabling the detection of functional alterations in the brain. PET utilises radiolabelled tracers to localise diseased tissue by detecting the gamma rays produced when positive and negative electrons meet, thereby elucidating the distribution and deposition of amyloid. After the neurotoxicity of oligomers has been demonstrated, novel imaging agents need to be developed in order to detect the cumulate soluble oligomers in the brains of AD patients [19]. Compared to traditional small molecule markers, mAb markers tend to bind specifically to target proteins, resulting in more precise imaging results. MAb158 is a mouse mAb that has been shown to specifically recognise Aβ protofibrils, with minimal binding affinity for monomeric and amyloid precursor proteins [19]. The humanised version of mAb158 is known as Lecanemab (BAN2401). In clinical Phase II and Phase III tests, it was shown to preferentially bind to soluble Aβ protofibrils, while having a lower affinity for insoluble plaques. Compared to aducanumab, Lecanemab has a significantly higher binding affinity for both small and large protofibrils [20].

3.2. Aβ mAbs in the Past and Future

The development of the Aβ mAbs has not been plain sailing. Many drugs have successfully completed in vitro and rodent trials but failed to meet the efficacy and safety standards required for approval in clinical trials. Gantenerumab was developed in 2000 due to its distinct binding affinity, it binds to the N-terminal portions of Aβ and the central portions of fibrillar Aβ, which makes it targeted for both soluble oligomers and insoluble fibrils/plaques. The same as aducanumab and lecanemab, gantenerumab is a humanised IgG1 antibody drug that removes Aβ depositions by activating the phagocytosis of microglia, preventing further aggregation of Aβ oligomers to the plaque [21]. Gantenerumab showed promising effects on reducing the level of p-tau and neurogranin in CSF, proving its potential efficacy for AD treatment. Moreover, gantenerumab is the first Aβ mAb administered by subcutaneous formulation, which is different from most of the mAbs that are given intravenously [21]. Despite the success in phase 1 and 2 trials, the GRADUATE I and II trials of gantenerumab in phase 3 failed to show a strong therapeutic effect [20].

Similar to gantenerumab, bapineuzumab has also shown effectiveness in reducing the levels of p-tau and other AD biomarkers, while failing to present clinically meaningful results due to the absence of restoration of cognitive function [22]. Bapineuzumab is the first Aβ mAb that proceeds to the phase 3 trials, binding with the N-terminus of the Aβ with the highest affinity to the toxic oligomers [23]. It also first reveals the most common side effects in mAb therapies which are called amyloid-related imaging abnormalities (ARIA). ARIA-oedema (ARIA-E) is defined as oedema in the grey and white matter of the brain and fluid in the sulci. ARIA-haemorrhage (ARIA-H), on the other hand, shows microhaemorrhages and pigmentation in the brain parenchyma. These side effects are mainly due to cerebral amyloid vasculopathy as Aβ mAbs remove the amyloid deposits, increasing the permeability of the blood vessels and making the proteinaceous fluid and red blood cells more susceptible to extravasation [24].

Given the results of previous studies, the Donanemab, which is currently in phase 3 of development and has shown strong positive outcomes, was designed to bind to a novel target called AβpE3. AβpE3 is a N-terminally truncated Aβ with specific pyroglutamate modification, it was observed to be considerably deposited in the brain as oligomers [25]. Donanemab has shown its unique ability to remove AβpE3 deposits in the CNS and prevent consequent amyloid aggregation. It has passed the safety and tolerance assessment in phase 1 trials including long-term and high-dose exposure which is the same as the previous Aβ mAbs. In the TRAILBLAZER-ALZ 2 trial, after 76 weeks of treatment, plaque levels in the brain were significantly decreased in patients who had used Donanemab compared to the placebo group, revealing its effective Aβ clearance effect [26]. In 2024, Donanemab became the third Aβ mAbs approved by the FDA.

4. Small Molecular Drugs in AD Therapies

In contrast to Aβ mAbs, the acetylcholinesterase inhibitors (AChEIs) were approved in the early years to treat AD and still play an important role in clinical use today. The most commonly used AChEI is donepezil, compared with galantamine and rivastigmine which were also approved for AD treatments, recent assessments indicated that donepezil generally has lower side effects [27]. The decrease of cholinergic neurones in AD patients reduced the levels of acetylcholine signalling. The inhibition of acetylcholinesterase has been shown to upregulate acetylcholine in the brain, thereby improving cognitive and memory functions [28]. This treatment relies on the patient's own number of cholinergic neurons, although it can provide significant symptomatic relief, it does not slow down the progression of the disease. Currently, donepezil is mainly used in the treatment of early to mid-stage AD disease, and it was approved for use in the treatment of severe Alzheimer's disease in 2006 [29].

Memantine is an uncompetitive NMDA receptor antagonist. Different from AChEIs, it partially blocks extrasynaptic NMDA receptors and regulates glutamate signalling levels in the brain, thereby protecting neurons from overexcitation and damage. NMDA receptors can mediate the transmission of sodium and calcium across neuronal synapses and are also considered to play a role in synaptic plasticity. High-affinity NMDAR antagonists such as ketamine would block the receptor for an extended period, which could impair learning and memory function. Conversely, the low affinity of memantine allows it to take effect only when the synaptic gap glutamate concentration is abnormally elevated, making it a suitable treatment for AD with good tolerance [30]. Memantine was developed by Merz Pharmaceuticals and approved by the FDA in 2003. It can be used alone or in combination with AChEIs. Same as donepezil, memantine can only be effective in symptomatic treatment, rather than impede the progression of the disease.

5. Future Trends

Recent studies have shown that the cause of AD may be related to damage to the blood-brain barrier (BBB). BBB leakage has been demonstrated to be higher in patients with early AD than in control groups. In the brains of AD patients, the extent of BBB damage was proportional to the amount of Aβ deposited [31]. Neuroimaging findings suggest that the glucose uptake in the brain is reduced in AD patients. Brain glucose uptake is dependent on glucose transporter 1 (GLUT1) at the BBB, supporting the fact that the BBB is damaged in people with Alzheimer's disease [32]. The reasons for BBB damage are multifactorial, including natural age-related changes, disease causes and ApoE4. In experiments, mice carrying the ApoE4 gene showed BBB leakage from the cortex and hippocampus compared to ApoE3 controls, a change that occurred before the appearance of Aβ deposition [33]. Aβ deposition has been widely recognised as one of the main causes of Alzheimer's disease. Recent studies have shown that Aβ has antimicrobial effects and is therefore likely to be an immune response for cleaning up microbial invasions induced by BBB damage, known as the antimicrobial protection hypothesis [34].

In clinical diagnosis, highly accurate blood tests have been demonstrated to have similar or even higher accuracy than CFT, which will allow it to be used in clinical diagnosis in the future [35]. CSF

tests usually require a lumbar puncture or lateral ventricular puncture to obtain the testing sample, local anaesthesia and more complex pre-operative preparation are also required. It is costly and time-consuming. For patients presenting with mild or asymptomatic symptoms, blood testing can be more acceptable. Aβ Mabs therapy, in combination with blood tests, may be able to detect and control AD progression earlier.

6. Conclusion

From aducanumab's FDA approval in controversy to lecanemab and donenamab's successive demonstration of robust clinical trial data, the future of Aβ mAbs appears to be getting brighter. The successive failures of earlier generations of Aβ mAbs drugs have promoted a re-evaluation of the Aβ hypothesis. However, these failures are consistent with the complex pathogenesis of AD, in which neurodegenerative damage in patients is the result of a combination of causes. Amyloid deposition is one of the most notable phenotypes, but other factors, such as neuroinflammation induced by the hyperphosphorylation of tau proteins, also play a role.

The ability of Aβ mAbs to remove amyloid has been successively proven in rodent experiments and clinical trials, and more challenges have arisen after the new generation of mAbs has been approved and formally used in the clinic. In addition to providing effective treatment, ways to reduce the burden on families and society are also of great importance. Compared to existing donepezil and memantine, Aβ mAbs do not present irreplaceable advantages in terms of administration and cost. Moreover, they have limited efficacy for the mid-to late-stage treatment period. The advancement of diagnostic methodologies is also of considerable significance, given that the aggregation of Aβ deposits occurs decades before the observable onset of clinical symptoms. In addition, in the clinical application of Aβ mAbs, how to reduce the side effects including ARIA-E and ARIA-H, and how to rebuild the damaged nerve cells and restore the cognitive and memory ability of the patients remains a challenge for the future.

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