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Research Progress of Aβ Targeted Therapy in Clinical Application of Alzheimer's Disease

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Abstract. Alzheimer'sdisease (AD) is a progressive neurodegenerative disease that poses a major health challenge to the aging global population. It is characterized by a progressive loss of cognitive functions, including memory, thinking, and behavioral abilities. Current literature shows that there is a critical gap in effective treatment options, as there are no widely accepted treatments that modify disease progression. This gap becomes increasingly important as the prevalence of AD increases. This article analyzes the application of Aβ-targeted therapy in AD, focuses on evaluating the impact of Lecanemab on cognitive function, and comprehensively evaluates the efficacy and safety of the treatment strategy. Study results show that Lecanemab can significantly reduce Aβ plaque burden and improve cognitive function in early-stage AD patients. The significance of this study is to provide a new direction for future AD treatment, and also points out safety issues that still need to be solved in current clinical practice. Future research can focus on improving the biological specificity of monoclonal antibodies and improving the safety of drugs to promote the development of AD treatment.

Keywords: Alzheimer's disease; Aβ; lecanemab.

1. Introduction

AD is a progressive neurodegenerative disease and one of the major health challenges faced by the elderly worldwide. It is characterized by a gradual decline in cognitive function (including memory and behavior). Due to the current lack of widely used drugs There are no drug therapies to improve the condition [1], and there is no radical treatment [2]. As the global population ages, the incidence of AD continues to increase, posing a significant burden to society and the medical system.

The complexity of AD is not only reflected in the diversity of its clinical manifestations, but also in its multiple potential pathological mechanisms. Different pathological mechanisms have different hypotheses, such as the abnormal phosphorylation hypothesis of Tau protein [3] and amyloid-βprotein (Aβ) hypothesis [4] and other hypotheses. Among these pathological mechanisms, the Aβ cascade hypothesis has always been the center of AD research. Although the exact cause of AD has not been fully elucidated, the Aβ cascade hypothesis is currently one of the most widely accepted pathogenesis mechanisms. This hypothesis believes that Abnormal deposition of Aβ in the brain is a key factor in the pathogenesis of AD. Aβ is produced by amyloid precursor protein (APP) through a series of enzymatic reactions. Its abnormal accumulation may lead to neuronal dysfunction and death. Abnormal accumulation of Aβ is a key factor in the pathogenesis of AD. Although the Aβ cascade hypothesis is controversial in academic circles, in the past five years, targeted treatment strategies targeting Aβ have shown the potential to slow down the progression of AD in clinical trials.

Among the treatment strategies for AD, Aβ-targeted therapy has always been a hot research topic. Strategies for Aβ-targeted therapy mainly include reducing the formation of Aβ, increasing the degradation and clearance of Aβ, neutralizing soluble Aβ oligomers, and directly inhibiting Aβ aggregation. In recent years, with the in-depth understanding of the role of Aβ in AD, targeted treatment strategies for Aβ have made significant progress. In particular, the development of Aβ monoclonal antibody (mAb) drugs, such as Lecanemab and Aducanumab, has shown potential to slow the progression of AD by clearing Aβ deposits in the brain. Lecanemab is an antibody targeting Aβ soluble aggregates. The results of its Phase III clinical trial showed that it can significantly slow

down the cognitive decline of early-stage AD patients, which brings new hope for disease-modifying treatment of AD.

Research on Aβ-targeted therapy is of great significance for understanding the pathogenesis of AD and developing new treatments. With a deeper understanding of the biological properties of Aβ and its role in AD, researchers can more precisely design drugs in order to achieve better therapeutic effects. In addition, successful cases of Aβ-targeted therapy have also provided new ideas and strategies for the treatment of other neurodegenerative diseases. With the continuous emergence of new drugs and the continuous optimization of treatment strategies, the treatment prospects for AD patients appear increasingly brighter.

This study will conduct an in-depth analysis of the application of Aβ-targeted therapy in the treatment of AD, focusing on evaluating the impact of Aβ-targeted therapy drugs on the cognitive function of AD patients, and comprehensively evaluating the efficacy and safety of treatment strategies, with a focus on mAbs. The drug Lecanemab. and discuss the challenges faced in clinical practice. By analyzing existing clinical trial data and drug action mechanisms, we can provide a comprehensive reference for future research directions and treatments.

2. Research Progress

2.1. Past Progress

In early research, the development of Aβ-targeted therapeutic drugs was not smooth sailing. Aβ vaccine AN1792 was the first Aβ vaccine to enter clinical trials. However, the clinical trials of Aβ vaccine AN-1792 were terminated early due to safety issues (such as the occurrence of subacute aseptic meningoencephalitis) [5]. Subsequently, researchers developed second-generation active immunotherapy vaccines, such as ACC-001, CAD106, Aβ vaccines, etc. These vaccines are designed to avoid the Th1 inflammatory response induced by activating one's own T cells, but these Aβ antibody drugs are It also failed to show the expected efficacy in clinical trials, and is still showing adverse reactions in clinical trials.

2.2. Current Progress

In recent years, Aβ-targeted therapy has made significant progress. For example, two drugs, aducanumab and lecanemab, have been approved by the FDA to slow the progression of the disease by reducing Aβ deposition. In addition, lecanemab has been shown to improve cognitive function in studies [6], and about 80% of patients have been cleared of Aβ from their brains.

2.3. Future Progress

Based on past and current research and summarizing experience, scientists can be reminded that in-depth research is still needed on the mechanism and clinical application of Aβ targeted therapy. Future research may be on how to improve the biological specificity of mAbs, such as targeting specific forms of Aβ oligomers, to provide more precise Aβ-targeted treatments. Issues such as how to improve the blood-brain barrier penetration of drugs and how to balance efficacy and safety are key directions for future research.

3. Aβ Hypothesis and Tau Hypothesis

The Aβ hypothesis and Tau hypothesis account for half of AD, and this article mainly focuses on the pathological role of Aβ in AD.

Histopathological features of AD indeed include extracellular deposition of Aβ and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein. Although both protein abnormalities are critical in AD, the Aβ hypothesis and the tau protein hypothesis focus on different aspects of their role and impact in the disease.

The Aβ hypothesis holds that abnormal accumulation of Aβ is the initial and core event in the pathogenesis of AD. Aβ is a polypeptide produced by amyloid precursor protein (APP) after specific enzyme cleavage. Under normal circumstances, Aβ can be cleared, but in AD patients, the production and clearance of Aβ are imbalanced, leading to its excessive accumulation in the brain. The deposition of Aβ forms senile plaques, which are thought to disrupt connections between neurons, leading to neuroinflammation and oxidative stress, and ultimately neuronal damage and death.

The Tau protein hypothesis focuses on the abnormal phosphorylation and aggregation of tau protein. The Tau protein hypothesis suggests that in healthy brains, tau protein helps maintain the stability of microtubules within nerve cells, thus supporting the structure and function of nerve cells. In AD, tau protein loses its normal function after being hyperphosphorylated and begins to form tangles within cells. These tangles destroy microtubules and affect the transport system of nerve cells, leading to loss of cell function and eventual cell death. The two are not mutually exclusive, therefore, focusing solely on the role of Aβ or tau in AD lesions, while ignoring the interaction between Aβ and tau, may not be entirely correct [7, 8]. They may interact and influence in the pathological process of AD. The accumulation of Aβ may promote tau protein phosphorylation and neurodegenerative changes, while abnormal aggregation of tau protein may also affect the clearance of Aβ. Therefore, the pathogenesis of AD may involve a complex interaction of multiple factors and pathways.

4. Biological Characteristics and Pathogenic Mechanisms of AB

The biological characteristics of Aβ include its multiple aggregated forms, such as monomers, oligomers, fibrils, and fibrillar aggregates, among which oligomers are considered to have higher toxicity and pathological relevance. Aβ oligomers can affect synaptic plasticity of neurons, leading to impairment of memory and cognitive functions. For example, Aβ oligomers can be isolated directly from the brains of Alzheimer's patients and have been shown to impair synaptic plasticity and memory [9]. The pathogenic mechanism of Aβ mainly involves the following four aspects:

1) The aggregation and plaque formation of Aβ lead to acidification of the microenvironment and increased oxidative stress, thereby damaging neuronal function.

2) Aβ binds to receptors on the cell membrane, such as interacting with NMDA receptors, affecting the homeostasis of calcium ions, leading to excitotoxicity.

3) Aβ activates microglia, triggers neuroinflammatory responses, releases inflammatory mediators, and aggravates nerve damage.

4) Aβ interferes with intracellular signaling by affecting the metabolism and energy supply of neurons, leading to cell dysfunction and death.

5. Development of Aβ-targeted Treatment Strategies: mAb Drug Lecanemab

Research into the mAb class of drugs targeting Aβ began in the 1990s. These drugs are based on the amyloid hypothesis and are designed to eliminate Aβ amyloid deposits in the brain. Bapineuzumab is one of the first Aβ mAb drugs developed to target mature amyloid deposits. Although it performed well in terms of efficacy, the drug was not approved by the FDA due to its insignificant impact on cognition, although it reduced amyloid plaque deposition in the brain and had some improvement in function [10].

Aducanumab is the first Aβ mAb drug approved by the FDA. Primarily targets amyloid plaques, but also binds Aβ oligomers. Aducanumab activates microglia and removes amyloid plaques through an immune response, thereby reducing the resulting accumulation of neuroinflammatory responses. In 2021, the approval of Aducanumab sparked some controversy in the academic and medical communities. This is largely due to the difference in phase III clinical results between the EMERGE and ENGAGE trials [11], whereas the primary target for lecanemab development was soluble Aβ oligomers. Its results in the CLARITY AD trial were even better [12]. Aβ oligomers rapidly and

reversibly interfere with memory behavior, interfere with synaptic circuit function, and reduce long-term potentiation (LTP) in the rat hippocampus. [13]. Existing studies widely believe that LTP function is a central mechanism. Storing information in the brain. Inhibition of LTP has been shown to lead to decreased cognitive and memory function. Results from in vivo experiments suggest that oligomers may be more suitable than other markers for disease progression detection [14].

Positron emission tomography (PET) has become a well-established method for diagnosing AD and can detect changes in brain function. Positron emission tomography uses radioactively labeled tracers to locate diseased tissue by detecting gamma rays. Produced when electrons and positrons meet, they shed light on the distribution and deposition of amyloid. The neurotoxicity of oligomers has since been demonstrated, necessitating the development of new imaging agents that can detect the accumulation of soluble oligomers in the brains of AD patients. Compared with traditional small molecule markers, mAb markers tend to specifically bind to target proteins, resulting in more precise imaging results. mAb158 is a mouse mAb that has been shown to specifically recognize Aβ fibrils, with the lowest binding affinity to monomeric and amyloid precursor proteins. The humanized version of mAb158 is called Lecanemab (BAN2401). Clinical Phase II and III trials have shown that it preferentially binds to soluble Aβ fibrils while targeting insoluble plaques with lower affinity. Compared with aducanumab, lecanemab has a 100-fold higher binding affinity for small fibrils and a 25-fold higher binding affinity for large fibrils [15].

MAbs are usually composed of four polypeptide chains. The two light chains are connected by disulfide bonds through the heavy chain to form a Y-shaped structure. The N-terminus is called the fragment antigen-binding (Fab) region and is responsible for recognizing and binding the antigen. The C-terminus, known as the fragment crystallization region (Fc region), is responsible for binding immune cells and triggering immune effector functions. Lecanemab is an adultized mAb directed against IgG1 (immunoglobulin G1). IgG is one of the most common types of antibodies.

In the human body, it is widely present in blood and body fluids with high specificity and extended half-life.

The four IgG subtypes are IgG1, IgG2, IgG3 and IgG4. IgG1 is the predominant one and usually exhibits strong responses to protein antigens. The Fc region of IgG1 can bind to natural killer cells and promote the release of cytotoxic substances, such as perforin, to produce antibody-dependent cell-mediated cytotoxicity. This property makes the Fc region of IgG1 a common therapeutic approach for treating diseases such as cancer.

6. Progress in Clinical Trials of Aβ: Taking Lecanemab as An Example

6.1. Clinical Trial Design and Results of Aβ-targeted Therapeutic Drugs

Lecanemab has shown positive results in improving cognitive function in patients with early-stage AD. Lecanemab's efficacy and safety have been evaluated in multiple clinical trials. An 18-month multicenter, double-blind, placebo-controlled phase 2 study of early AD, including 854 patients with early AD (Lecanemab, 609; placebo, 245), the results showed that Lecanemab significantly reduced Aβ plaque burden [16].

6.2. Clinical Development Mechanism

Anti-amyloid antibodies are given to animals by injection in preclinical development or by infusion to AD patients in clinical trials. Once inside the body, the antibodies effectively remove amyloid in the body and brain. And antibodies have the potential to promote the clearance of amyloid before it forms plaques. Antibodies can bind to established plaque. Antibodies can trigger immune cells to clear amyloid and activate immune cells to eliminate amyloid.

6.3. Experimental Results

Patients experienced significant improvements in clinical outcomes in terms of cognition, function, and activities of daily living. These results support and demonstrate the potential clinical benefit of lecanemab in improving cognitive and functional outcomes in patients with AD. Another group of teams conducted a systematic review and meta-analysis on the cognitive effectiveness and safety of Lecanemab in AD patients [16]. They screened literature published on various large literature websites such as PubMed before February 2023, looking for randomized controlled trials testing Lecanemab in the treatment of cognitive decline in patients with mild cognitive impairment (MCI) or AD [17]. Results: A total of four randomized controlled trials involving 3108 AD patients (1695 in the Lecanemab group and 1413 in the placebo group) were included to synthesize the evidence. Baseline characteristics of the two groups were similar across all outcomes, with the only differences being ApoE4 status and higher MMSE scores observed in the Lecanemab group. According to reports, Lecanemab's Clinical Dementia Rating-Sum-of-Boxes (CDR-SB) in patients with early-stage AD Stabilizing or slowing the decline is beneficial [17].

6.4. Experimental Conclusion

Their analysis found that lecanemab demonstrated significant positive statistical effects on cognition, function, and behavior in patients with early AD [1]. Consistent results across studies confirm the robustness of these findings. Another meta-analysis showed that lecanemab administered at a dose of 10 mg/kg every two weeks was associated with positive effects on cognitive outcomes measured by various parameters in individuals with AD. These results provide valuable insights into the potential effectiveness of lecanemab as an intervention to treat cognitive impairment in this patient population [18].

6.5. Issues and Challenges

While the results from the Phase 3 trial are certainly encouraging, there are still many unanswered questions about lecanemab and its ability to treat AD [4]. An important question is whether the benefits seen in phase 3 trials will translate into improved clinical outcomes for patients [18]. Another concern is whether lecanemab will be beneficial in patients with higher-grade AD, where the pathology is more severe and extensive.

6.6. Security Question

Although there was no strong evidence of significant differences in the occurrence of treatment-emergent adverse events (TEAEs), the meta-analysis raised concerns about ARIA-E (amyloid-related imaging abnormality-edema) and There is a significant safety concern regarding the increased risk of ARIA-H (amyloid-related imaging abnormality-hemorrhage). In particular, the increased risk of ARIA-H underscores the importance of careful consideration and monitoring of the safety profile of lecanemab in clinical practice. In the CLARITYAD trial, adverse events resulted in 6.9% of lecanemab participants withdrawing from the trial, compared with 2.9% in the placebo group. The most common adverse event (>10%) in the lecanemab group was infusion reaction (Lecanemab: 26.4%; placebo: 7.4%). Most of these reactions were mild to moderate (Grade 1-2: 96%) and occurred mainly with the first dose (75%). The lecanemab arm also had a higher incidence of ARIA, which is related to the recognition of this type of therapy - it is classified as ARIA-H (including cerebral microbleeds, major cerebral hemorrhages, and superficial cerebral hemorrhages). Iron deposition: Lecanemab 16.9%; placebo 8.9%) and ARIA-E (edema/exudation: Lecanemab 12.6%; placebo 1.7%) [19].

Furthermore, the correlation between amyloid-beta clearance and slowing of cognitive decline has not yet been established. Lecanemab may not slow cognitive decline to an extent that is clinically significant. Lecanemab has different effects on patients with different ApoE genotypes. Lecanemab may cause ARIA.

7. Conclusion

This paper provides an in-depth analysis of Aβ-targeted therapy in AD, with special attention to the application of the mAb Lecanemab and its impact on cognitive function. Studies have shown that Lecanemab significantly reduced Aβ plaque burden and improved patients' cognitive function in early-stage AD patients, which provides new hope for disease-modifying treatment of AD.

The pathogenesis of AD is complex, in which Aβ accumulation is considered to be one of the core factors. Although abnormal phosphorylation of Tau protein is equally important, this study mainly focused on the role of Aβ and its targeted therapeutic strategies. Lecanemab, a mAb directed against Aβ soluble aggregates, has shown the potential to slow the progression of AD by clearing Aβ deposits in the brain. Research data shows that in multiple clinical trials, Lecanemab not only effectively reduced the burden of Aβ, but also showed significant improvements in cognitive function tests, which is particularly important for early-stage AD patients. However, although Lecanemab has shown positive clinical effects, there are also some safety issues that need to be resolved. The study noted that lecanemab is associated with an increased risk of ARIA, specifically ARIA-E (edema) and ARIA-H (bleeding), making monitoring and management of patients in clinical practice particularly important. In addition, the incidence of adverse reactions is relatively high, especially in the early stages of treatment, and patients need to be properly guided and observed. Overall, the research results of Lecanemab provide a new direction for the treatment of AD, but further research is still needed to resolve existing safety and efficacy issues before clinical promotion. Future research should focus on improving the biological specificity of mAbs, improving the safety of the drugs, and exploring differences in the response to treatment in patients with different genotypes. These efforts will help advance the treatment of AD and ultimately improve patients' quality of life.

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