

Advances in Antibody Therapy for Alzheimer's Disease

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Abstract: Alzheimer's Disease (AD) is a progressive neurodegenerative disease characterized by cognitive decline and memory impairment. Its main pathological hallmarks include β -amyloid ($A\beta$) plaque deposition and abnormal tau protein aggregation. In recent years, antibody therapy against $A\beta$ and tau proteins has emerged as an important direction in AD therapeutic research due to its high specificity and clear mechanism of action. This paper reviews the mechanism of action of $A\beta$ monoclonal antibodies, including their roles in $A\beta$ clearance, immune system activation and blood-brain barrier regulation. Additionally, this paper discusses the latest advances in antibody therapy, including approved drugs and drug candidates in clinical trials. The findings indicate that although antibody therapy has slowed the progression of AD to a certain extent, it still presents many challenges in terms of cognitive improvement, safety and clinical trial design. Future research directions include multi-target combination therapy, precision medicine, and early intervention to improve the effectiveness and safety of antibody therapy.

Keywords: Alzheimer's disease, antibody therapy, monoclonal antibody, β -amyloid, tau protein

1. Introduction

Alzheimer's Disease (AD) is one of the most common neurodegenerative diseases worldwide, mainly characterized by progressive cognitive impairment, memory loss, and behavioral dysfunction, which seriously affects the quality of life of patients and their families. The World Health Organization (WHO) predicts that with the accelerated aging of the global population, the number of AD patients will increase significantly in the coming decades, bringing a huge economic burden to the society. Therefore, it is urgent to find effective treatments.

The typical pathology of AD includes neurofibrillary tangles (NFTs) caused by the deposition of amyloid-beta ($A\beta$) plaques and abnormal aggregation of tau protein in the brain. Although the specific pathogenesis of AD remains unclear, increasing evidence suggests that reducing or removing $A\beta$ and tau protein aggregates in the brain may help improve pathological symptoms and cognitive function.

In recent years, antibody therapy has become an important frontier in AD drug development due to its high specificity and clear mechanism of action. Several monoclonal antibodies targeting $A\beta$ have progressed through clinical research, with some, such as donemab and leucaneumab, receiving FDA approval. However, their actual clinical effects and safety are still controversial [1]. In addition, some progress has been made in the development of tau protein antibodies, but they have

not yet achieved definitive clinical success, and their potential for use in combination therapies needs to be explored in depth in the future.

This paper systematically review the mechanism of action of antibody therapy, discusses its latest clinical research progress and existing challenges, and further proposes directions to improve the therapeutic regimen, aiming to providing a theoretical basis and practical guidance for the pharmacological treatment of Alzheimer's disease.

2. Mechanism of action of antibody therapy

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by pathological changes, including the formation of β -amyloid ($A\beta$) plaques and abnormal aggregation of tau protein. Antibody therapeutic strategies targeting these core pathologic markers aim to slow disease progression by reducing plaque deposition and alleviating neuroinflammatory responses.

2.1. Targeting $A\beta$ plaque clearance

Accumulation of $A\beta$ plaques is considered one of the main pathological features of AD. Anti- $A\beta$ monoclonal antibodies act through multiple mechanisms. First, they can directly bind to $A\beta$ monomers or aggregates, preventing their deposition into plaques. For example, antibodies such as lencanemab (Lecanemab) and donemab (Donanemab) reduce the deposition of $A\beta$ in the brain by specifically binding to it. Second, upon binding to $A\beta$, these antibodies activate the immune system and promote phagocytosis and clearance of $A\beta$ by immune cells such as microglia. However, this immune activation may trigger an inflammatory response, leading to side effects such as amyloid-related imaging abnormalities (ARIA). In addition, antibody therapy may accelerate the exocytosis of $A\beta$ from the brain by altering the gradient of $A\beta$ concentration inside and outside the blood-brain barrier, thereby enhancing its clearance efficiency. Overall, these mechanisms work together to help slow down the disease progression of AD [2].

2.2. Targeting tau proteins and other pathological processes

Although $A\beta$ plaques are considered a key pathogenic factor in AD, there is growing evidence that abnormal aggregation of tau proteins plays an equally important role in neurodegenerative damage. As a result, some antibody therapies have begun to target tau proteins.

First, anti-tau monoclonal antibodies reduce the formation of neurofibrillary tangles (NFTs) by blocking the aberrant aggregation of tau proteins or facilitating their clearance. However, to date, no anti-tau antibody drug has have received marketing approval, and its clinical efficacy remains to be further validated. Second, a multi-targeted therapeutic strategy combining anti- $A\beta$ and anti-tau therapies may provide superior therapeutic efficacy in improving AD pathology. This strategy aims to intervene in multiple pathogenic pathways simultaneously, thus potentially slowing disease progression more effectively. By combining these two approaches, future treatments may become more comprehensive and effective.

3. Progress in clinical research

3.1. Antibody therapies against Beta Amyloid ($A\beta$)

Representative drugs currently used for anti- $A\beta$ antibody therapy in Alzheimer's disease (AD) include aducanumab (Aduhelm), lencanumab (Lecanemab), and donemab (Donanemab).

Aducanumab was withdrawn from the market in early 2024 due to questionable efficacy and safety concerns, such as amyloid-related imaging abnormalities (ARIA), despite early FDA approval. Lencanumab, co-developed by Eisai and Bojen, specifically recognizes the $A\beta$ fiber structure,

significantly reduces A β load, improves cognitive function in early AD patients, and has received formal FDA approval. Donemab, developed by Eli Lilly and Company, selectively targets A β aggregates, effectively removes plaques from the brain, significantly slowing down cognitive decline. It has received accelerated approval from the FDA in 2023 [3].

Potential drugs still under investigation include Trontinemab (R&D code: RG6102), developed by Roche for the treatment of Alzheimer's disease. The drug is based on the anti-amyloid monoclonal antibody gantenerumab and utilizes Roche's Brainshuttle technology, which facilitates the antibody's crossing of the blood-brain barrier by binding the antibody to transferrin receptor 1 (TFR1), thereby increasing the concentration of the drug in the brain. Compared to conventional antibodies, trontinemab using Brainshuttle technology was eight times more concentrated in the cerebrospinal fluid than gantenerumab, enhancing its ability to cross the blood-brain barrier.

In a Phase 1b/2a clinical trial, trontinemab showed significant results in clearing amyloid plaques from the brains of patients with Alzheimer's disease. However, the trial also included a serious adverse event in which a patient died. A 78-year-old female patient died on day 44 from a right frontal lobe brain hemorrhage. Further analysis showed that the patient may have had signs of cerebral amyloid angiopathy (CAA), a condition in which amyloid accumulates in the walls of cerebral arteries and may increase the risk of hemorrhage [4].

Despite these adverse events, Roche plans to initiate a Phase III clinical trial in 2025, expected to be completed in 2028. If the trial results are positive, trontinemab may represent a significant breakthrough in the field of Alzheimer's disease treatment.

3.2. Antibody therapies against tau protein

Currently, no anti-tau monoclonal antibodies have received marketing approval [5]. There have been attempts to develop drugs including Zagotenemab (LY3303560), developed by Eli Lilly, targeting the N-terminal region of tau protein. However, it failed to show effectiveness in a Phase II clinical trial in 2021, leading to program termination. Tilavonemab (ABBV-8E12), developed by AbbVie, targets the intermediate structural domain of tau protein. Although it showed some safety in early trials, the primary endpoint was not met in a Phase II clinical trial in 2020 and the program was terminated [6]. Gosuranemab (BIIB092), developed by Bojen (Biogen), targets the N-terminal region of tau proteins and aims to stop their propagation. However, failure to meet the primary endpoint in a Phase II clinical trial in 2021 led to the termination of the program. Semorinemab is a monoclonal antibody developed by AC Immune in conjunction with Genentech designed to target tau proteins for the treatment of Alzheimer's disease (AD). The antibody works by binding to the N-terminal region of tau proteins, preventing their abnormal aggregation and propagation. Despite some positive results in the LAURIET trial, development of semorinemab was terminated in February 2024 for failing to show significant efficacy in other key metrics [7].

Currently in development, RI-AG03 is a novel peptide inhibitor specifically designed to block the aberrant aggregation of Tau proteins for treating neurodegenerative disorders such as Alzheimer's disease. RI-AG03 is dual-targeted and is able to act simultaneously on the two main aggregation-promoting hotspots on Tau proteins ($^{\wedge}306VQIVYK^{\wedge}311$ and $^{\wedge}275VQIINK^{\wedge}280$), a property not yet realized by other inhibitors. It was shown that RI-AG03 effectively inhibited the aggregation of multiple Tau proteins in in vitro experiments and exhibited inhibition of neurodegeneration and prolongation of lifespan in a *Drosophila* model. In addition, RI-AG03 was able to penetrate the cell membrane and enter the cell interior to bind to Tau proteins and prevent their aggregation. In the experiments, RI-AG03 was non-toxic to cells and showed good safety. These properties make RI-AG03 a promising disease-modifying drug candidate that warrants further study to evaluate its efficacy and safety in the treatment of Tau protein-related diseases such as Alzheimer's disease [8].

3.3. Future development trends

As the understanding of the pathogenesis of Alzheimer's disease (AD) continues to deepen, interventions such as antibody therapy are developing in a more scientific and individualized direction. Future advancements in AD treatment may follow these trends.

First, AD has significant individual differences, and its pathogenesis is closely related to the expression levels of A β and tau proteins, genetic background (e.g. APOE ϵ 4 allele) and other biomarkers. In the future, treatment strategies will pay more attention to precise diagnosis and typing, and tailor-made individualized antibody treatment plans based on the degree of A β deposition, abnormal expression of tau protein, cerebral metabolic status, and other imaging and fluid biomarkers to maximize efficacy, minimize side effects, and achieve the goal of "the right drug for the right patient".

Second, given that AD is a complex disease with multiple factors and pathways, it is difficult to achieve comprehensive control by relying only on a single target (e.g., A β or tau). The future trend is to develop "multi-target" or "combination therapy" programs, i.e., using anti-A β antibodies and anti-tau antibodies simultaneously, or combining drugs with other mechanisms of action (e.g., anti-inflammatory, antioxidant, regulation of cerebral blood flow, etc.) to synergistically regulate multiple pathological aspects [9]. Such strategies are expected to improve the overall therapeutic efficacy and delay the continued decline in cognitive function.

Third, many current antibody drugs have limited efficacy in patients with mid- to late-stage AD, suggesting that waiting until cognitive impairment is evident may be too late for treatment. Studies have shown that abnormal aggregation of A β plaques and tau proteins often occurs decades before the onset of clinical symptoms [10]. Therefore, in the future, AD treatment will pay more attention to early screening, early diagnosis and early intervention, especially in mild cognitive impairment (MCI) or asymptomatic but high-risk populations, and early removal of abnormal proteins and delayed neurological damage by antibody drugs are expected to significantly prolong the dementia-free period of patients.

Fourth, in addition to A β and tau proteins, neuroinflammation, synaptic dysfunction, mitochondrial damage, and brain-immune system imbalance are also believed to play important roles in AD pathogenesis. In the future, drug research and development will pay more attention to these new targets, and at the same time explore nanomedicine, blood-brain barrier penetration technology, single domain antibody (nanobody) and other new means of delivery, to improve therapeutic precision and intracerebral drug arrival efficiency.

Finally, the integration of digital medicine and remote monitoring technology can be realized. With the help of wearable devices, digital cognitive assessment tools and artificial intelligence algorithms, dynamic monitoring of AD patients' condition changes can be realized, providing continuous feedback and individualized adjustment suggestions for antibody therapy. This will significantly improve the controllability and response sensitivity of the treatment program.

4. Challenges and directions for improvement in clinical trials

Despite the breakthrough progress of antibody therapies in the field of Alzheimer's disease (AD), such as the successive approvals of donemumab and lecanumab, their clinical application still faces multiple challenges that limit their widespread dissemination and efficacy. In the future, there is a strong need for continued optimization in several areas.

First, the correlation between efficacy and pathologic improvement is insufficient. Clinical studies have shown that although antibody therapy can significantly reduce A β deposition in the brain, there are still some limitations in improving cognitive function [11]. This suggests that the pathogenesis of AD may go far beyond A β deposition, and that tau protein abnormalities, neuroinflammation, and

synaptic dysfunction also play important roles in the disease process. Therefore, a single treatment targeting A β may be difficult to fully reverse cognitive decline, and intervention strategies integrating multiple pathologic mechanisms are urgently needed in the future.

Second, clinical design bias affects efficacy assessment. Some trials used non-blinded design to make patients and physicians aware of the treatment grouping, which may have a psychological implication effect on the cognitive score results and reduce the objectivity and reliability of the data. In order to improve the quality of evidence, the design of randomized, double-blind, placebo-controlled, and other scientifically rigorous trials should be strengthened in the future to reduce human bias and ensure that the assessment of efficacy is more realistic and credible.

In addition, safety issues limit the sustainability of treatment. Antibody therapy is often associated with certain safety risks, including amyloid-related imaging abnormalities (ARIA), especially cerebral edema (ARIA-E) and microhemorrhage (ARIA-H), which most often occurs in ApoE ϵ 4 carriers, and may lead to symptoms such as headache, confusion, and even interruption of the treatment in severe cases. Immune-related adverse reactions, such as encephalitis, neuroinflammation, and systemic malaise, affect patient tolerance and adherence, limiting the potential for long-term drug use.

Future directions for improvement include several key areas to enhance the efficacy and safety of Alzheimer's disease (AD) antibody therapy. First, optimizing antibody molecular structure is an important direction. Through precision engineering modifications, specific recognition of A β or tau proteins can be improved, immune responses triggered by off-target binding can be reduced, and side effects can be reduced at the source.

Second, improving clinical trial protocols and adopting more scientific designs, such as double-blind placebo control and delayed treatment crossover design, can enhance the credibility of results and ensure ethics. Finally, the development of a biomarker screening system, by combining cerebrospinal fluid and blood biomarkers and imaging data, can accurately identify the patient groups most likely to benefit, thus improving the selectivity and individualization of treatment.

5. Conclusion

Alzheimer's disease is a highly complex neurodegenerative disease whose core pathologic mechanisms include A β plaque deposition and abnormal tau protein aggregation. In recent years, antibody therapy targeting A β and tau proteins has gradually become a key direction of therapeutic research due to its high specificity and clear mechanism. A β antibodies such as donemumab and lecanumab have been approved and marketed, showing certain pathological improvement effects and providing new hope for disease intervention. However, the efficacy of antibody therapy in improving cognitive function is still unsatisfactory, and there are safety issues, such as ARIA and immune-related adverse reactions, coupled with the bias in the design of some clinical trials, resulting in the reliability of efficacy assessment being compromised.

In the face of these challenges, the future development of antibody therapy should focus on more systematic and precise strategies. On the one hand, individualized treatment should be strengthened to improve the pertinence and effectiveness of therapeutic choices through biomarker screening and molecular typing; on the other hand, combined multi-targeted therapeutic strategies with integrated intervention of A β , tau protein and related inflammatory pathways may become an important way to improve therapeutic efficacy. Meanwhile, moving the therapeutic window forward to the early stage of the disease, especially to the stage of mild cognitive impairment, is expected to be more effective in slowing down the progression of the disease. In addition, optimization of drug delivery systems, such as enhancing blood-brain barrier permeability and reducing off-target responses, as well as more scientifically rigorous clinical trial design, are also key directions for improving the safety and quality of evidence for treatment in the future.

However, this paper has certain shortcomings, including the relatively limited discussion of emerging therapies and the lack of in-depth analysis on the assessment of long-term efficacy and patients' quality of life improvement. Looking forward, as multidisciplinary integration and technological advances continue to advance, it is expected that more efficient, safe, and personalized therapeutic strategies will emerge, leading to substantial advancements in the prevention and treatment of Alzheimer's disease.

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