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Review of the Monoclonal Antibody Drugs for the Treatment of Alzheimer's Disease

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Abstract. Alzheimer's Disease (AD) is A neurodegenerative disease characterized by progressive cognitive decline. Its pathological mechanism mainly involves the deposition of β-amyloid (Aβ) and abnormal phosphorylation of tau protein. In recent years, monoclonal antibody drugs targeting the pathological basis of AD have become the focus of research and treatment. This article reviews the latest progress in the use of monoclonal antibodies in the treatment of Alzheimer's disease, with a focus on the post-marketing treatment of Donanemab and Lecanemab and the development progress of three monoclonal antibodies in different clinical stages. Monoclonal antibody drugs aim to delay neurological deterioration and improve cognitive performance by targeting and removing pathological Aβ aggregates in the brain. However, safety issues such as brain edema and hemorrhage, as well as controversies on efficacy evaluation, are still facing practical application. In addition, in recent years, the development of combination therapy has attracted wide attention; that is, by combining monoclonal antibody drugs with traditional drugs to improve cognitive function, it is expected to achieve the dual effect of pathological clearance and symptom improvement. The potential advantages of nanobAbs as anti-AD drugs are also discussed.

Keywords: Alzheimer's disease, Monoclonal antibodies, β-Amyloid, Nanobodies, Cognitive improvement

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by a gradual cognitive decline and memory impairment. Its primary pathological features include abnormal β-amyloid (Aβ) plaque deposition and the formation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein, leading to neuronal damage and brain function decline [1]. The clinical manifestations are memory impairment and cognitive decline, etc. Finally, the patient's quality of life is reduced, which leads to various complications and death. With the accelerating global aging population, Alzheimer’s disease has become a significant challenge in global public health. In December 2024, 482,890 people over the age of 65 were officially diagnosed with AD in England, which is 4.2% of the 11.4 million people aged 65 [2].

However, current treatments for Alzheimer’s disease have demonstrated limited clinical efficacy. Most pharmacology is still focused on the excitability of the central system. In other words, this pharmacological process did not counter the abnormal deposition of β-amyloid plaques. When there

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is excessive deposition of beta-amyloid plaques. Consequently, such traditional approaches fail to halt or significantly slow disease progression, particularly during mid-to-late stages. In contrast, recent advancements in monoclonal antibody (mAb) therapies offer a promising alternative due to their high target specificity, superior therapeutic efficacy, and relatively fewer adverse effects compared to traditional treatments. More importantly, they make up for the shortcomings of traditional drugs in treating the root cause of the disease (β-amyloid). In theory, monoclonal antibody drugs will play a more significant role in the treatment of Alzheimer's disease. To provide new treatment options for Alzheimer's disease.

Currently, several monoclonal antibody therapies have successfully received clinical approval, and a small number of mAbs have successfully passed rigorous clinical trials and been approved for marketing in some countries and regions. In addition, great results have been achieved in the follow-up treatment report of patients. This article systematically analyzes the status of monoclonal antibodies in the treatment of Alzheimer's disease by analyzing the current drugs on the market, the mabs in development, and the prospect of new mabs therapies.

2. Marketed monoclonal antibodies for Alzheimer’s disease

2.1. Lecanemab

Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble fibrils, has shown promising therapeutic effects in patients with Alzheimer's disease. It is currently approved for clinical use in certain regions for treating Alzheimer’s disease (AD). Specifically, Lecanemab targets distinct regions of Aβ, particularly binding with high affinity to its N-terminal amino acid residues, thereby inhibiting the aggregation and promoting clearance of Aβ plaques [3]. Moreover, due to this targeted mechanism, the insoluble fibrillar forms of Aβ become more readily recognizable and clearable by immune cells [4-6].

In a double-blind, randomized, placebo-controlled, phase III study of this drug, a total of 1,795 participants were enrolled, with 898 patients randomly assigned to receive lecanemab at a dose of 10 mg/kg biweekly. At baseline, participants exhibited an average Clinical Dementia Rating-Sum of Boxes (CDR-SB) score of approximately 3.2. After 18 months of treatment, the mean change in the lecanemab group was 1.21, relative to a value of 1.66 in the placebo group [7]. Patients receiving lecanemab had improvements in cognition relative to placebo, demonstrating a modest effect in the early treatment of Alzheimer's patients. A significant difference was also found between lecanemab-treated and placebo-treated subjects concerning PET-detectable Aβ, with patients who received lecanemab having a significant decrease in PET-Aβ values compared with those in the placebo group [8].

However, treatment with lecanemab is associated with a known side effect known as Amyloid-Related Imaging Abnormalities—Edema (ARIA-E). ARIA-E refers to cerebral edema or exudation detected by magnetic resonance imaging (MRI) while receiving anti-amyloid therapy. This is because antibody drugs, by clearing amyloid deposits in the brain, may sometimes change the permeability of cerebral blood vessels, leading to abnormal accumulation of fluid in brain tissue, thereby causing the phenomenon of edema. Clinically, patients may experience adverse effects such as headaches or nausea. ARIA-E occurred in 12.6% of patients who used Lecanemab, and ARIA-H occurred in 17.3% [9]. However, the symptoms were mostly mild and did not interfere with the use of lecanemab.

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2.2. Donanemab

Donanemab is another humanized monoclonal antibody that targets β-amyloid deposits in patients with early symptomatic Alzheimer's disease [10]. Its therapeutic rationale is similar to that of Lecanemab. Its primary mechanism involves selectively binding and clearing cerebral β-amyloid plaques, thereby aiming to slow cognitive decline associated with AD progression.

A recent Phase III randomized, placebo-controlled clinical trial evaluated the therapeutic effectiveness and tolerability of Donanemab. Donanemab was administered intravenously at 0.1 mg/kg to 10 mg/kg versus placebo, followed by 12 weeks of follow-up at each dose level. Cognitive improvement classified by Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog-14), MMSE score, and obtained FCSRT-IR values were used during the period. Cognitive improvement was assessed at 24, 48, and 72 weeks after treatment initiation and after drug discontinuation [11].

Significant reductions in amyloid burden were observed through PET imaging. Patients treated with Donanemab mab had a 40-50% reduction in amyloid plaque levels and a mean SUVR change of − 0.36. The study also found that Donanemab continued to have a significant therapeutic effect at the other doses. Amyloid PET at week 24 revealed a 16.5CL reduction in the 10 mg/kg group and a 40.0CL reduction in the 20 mg/kg group. Moreover, a complete amyloid clearance threshold was achieved in 46 of 115 participants (40%) who were treated with Donanemab [12].

In terms of the drug's safety and tolerability, 6 patients (16.2%) had mild or moderate infusion reactions after receiving 2 to 3 doses. One patient was troubled by ARIA-E-related symptoms. ARIA-H occurred in two patients (4.4%) in the 10 and 20 mg/kg cohorts. The drug was well tolerated at a dose of 10 mg/kg, as determined by a comprehensive cut-off at 72 weeks. These results indicate that Donanemab can ensure significant efficacy while avoiding significant adverse reactions in patients.

The half-life of Donanemab mAb is estimated at 11.8 days, based on a two-compartment model with first-order elimination. The lower range is typically seen for human IgG1 and monoclonal antibodies in this class, which means that the drug fits the paradigm of normal metabolism of monoclonal antibodies out of the body and confirms the safety profile of this drug.

3. Monoclonal antibodies in clinical development

Currently, as more binding sites on the Alzheimer's disease marker Ab are revealed, more monoclonal antibody drugs are being developed. Many of these emerging antibodies have demonstrated promising therapeutic potential, often surpassing the efficacy of currently marketed drugs in early-stage clinical trials (Phase I to III). Nevertheless, challenges such as insufficient cognitive efficacy or safety concerns have hindered the progress of several programs.

3.1. Ponezumab: clinical development and limitations

Ponezumab, a monoclonal antibody developed by Eli Lilly, has achieved results in phase 1 and phase 2 clinical trials. Ponezumab targets humanized amyloid-ß, the same target as two mabs currently on the market. However, clinical progress for Ponezumab was severely hampered due to disruptions caused by the COVID-19 pandemic [13].

In a randomized, double-blind, single-dose, phase 1 clinical trial evaluating safety, pharmacokinetics, and pharmacodynamics, Ponezumab demonstrated acceptable safety profiles without any reported severe adverse events. Common mild adverse events included upper

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respiratory tract infection, headache, and back pain. Drug concentrations reached a maximum after 2 hour of intravenous infusion and subsequently decreased. Fortunately, no vasogenic edema or new microbleeds were reported, which is consistent with preclinical findings that probably address the problem of induction of this effect by current MAB agents. Because ponezumab targets the C-terminus of amino acid residues, it has A weak affinity for the plaque (or deposited) form of Aβ in the brain and vasculature, preventing vasogenic edema or microbleeds [14].

This program has not made much progress in recent years because its efficacy is not significant. Despite impressive amyloid reduction in a phase 2 clinical trial, evidence of translation into cognitive and functional improvements was limited. Some clinical trials have shown mild cognitive improvement or delayed cognitive decline, but the overall effect is controversial, and there are large discrepancies between early and mid-term efficacy trials in Alzheimer's disease, so the trials had to be stopped.

3.2. Semorinemab: clinical efficacy, safety, and challenges

Semorinemab is a monoclonal antibody developed by Roche that targets the tau protein. In Alzheimer's disease, tau proteins are abnormally phosphorylated and aggregated to form neurofibrillary tangles, leading to neuronal dysfunction and death. Semorinemab prevents tau binding, blocks its propagation between neurons, and potentially slowing or halting disease progression.

Semorinemab showed excellent tolerability and safety, as compared with placebo, in a phase 2, randomized, double-blind, placebo-controlled trial. The worrisome symptoms of vasogenic edema/sulcal effusion, superficial siderosis, and microbleeds were not present in this experiment. It also means that adverse effects of this target that are common in Alzheimer's mAbs are likely to be eliminated with the discovery of this target. Pharmacokinetic results showed that serum semorinemab concentrations were consistent with phase 1 data from healthy volunteers, and no semorinemab residues were found in patients compared with placebo. Semorinemab is metabolized out of the body during the normal cycle [15].

However, despite its favorable safety profile, Semorinemab faces critical challenges regarding clinical efficacy. Existing studies have shown that tau protein may exist in a variety of forms during cell-to-cell transmission, either in free form or through membrane-wrapped structures such as extracellular vesicles. This biological complexity makes it challenging for a single monoclonal antibody directed against the N-terminal region to completely remove abnormal tau species. This failed Semorinemab to demonstrate a significant effect on clinical improvement and inhibition of tau pathological accumulation [16].

Pharmacokinetic modeling has further identified a critical limitation: although Semorinemab achieves high concentrations and exhibits strong binding affinity to tau in peripheral circulation, the presence of the blood-brain barrier substantially limits its penetration into the central nervous system (CNS), specifically within neuronal synapses, where it is most therapeutically relevant. Although data suggest that Semorinemab binds well in the nerve periphery, inadequate levels of the antibody in the synaptic cleft of neurons may impair its clinical efficacy in blocking abnormal tau propagation.

3.3. The UB-311 vaccine

UB-311 is a synthetic peptide-based active immunotherapy designed to selectively target β-amyloid (Aβ) fibrils and oligomers, with minimal binding to Aβ monomers. This selective targeting

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facilitates the removal of neurotoxic aggregates while preserving the function of Aβ in normal physiological processes. And, to a lesser extent, targeted monomers. UB-311 comprises two proprietary synthetic helper T cell peptide epitopes (UBITh®), each formulated with Aβ attached (B cell epitope). This means that the drug mechanism can reduce the activity of T cells against amyloid. Therefore, the AIEH-E problem was avoided, and the drug was able to clear Ab while ensuring good tolerability and safety [17].

The therapeutic rationale behind UB-311 is based on active immunotherapy, utilizing the patient's immune system to generate antibodies against pathological forms of Aβ. A randomized, double-blind, placebo-controlled phase 2a clinical trial conducted over 78 weeks evaluated the safety, tolerability, and efficacy of UB-311 in patients with mild Alzheimer's disease. The vaccine was generally safe and well-tolerated, with only asymptomatic occurrences of ARIA-H, including hemosiderin deposits, such as microbleeds and superficial siderosis. Six serious adverse events were reported across six participants [18].

In efficacy analyses of cognitive, functional, behavioral, and global assessments, patients who completed UB-311 showed no significant slowing of improvement, and the results were not statistically significant compared with placebo. However, UB-311 achieved the highly reactive ability to target chronic endogenous proteins and triggered B-cell-mediated antibody production, a process that prevented the activation of T-cell cytotoxicity and, thus, prevented the development of ARIA-E. Although this trial did not perform as well as expected in terms of efficacy, patients who received the vaccine had substantial improvements in brain amyloid. It is suggested that the drug can be given in higher doses or more times under the premise of ensuring safety to achieve a higher therapeutic effect.

4. Future prospects and challenges

Researchers have recently been exploring diverse therapies for Alzheimer's disease, aiming to achieve better treatment effects. Traditional therapy combining traditional drugs with monoclonal antibodies has shown great potential in the treatment of Alzheimer's disease. The combination of traditional drugs and monoclonal antibody drugs can play a synergistic effect: Traditional drugs (such as cholinesterase inhibitors and NMDA receptor antagonists) are mainly used to improve patients' cognitive ability and daily function, while monoclonal antibody drugs can accurately remove amyloid beta protein, thereby delaying the progression of the disease. Different from the structure of traditional antibodies, nano-antibodies derived from camels or dogfish are more interesting to researchers. Compared with traditional antibodies, the monomeric structure of nanoantibodies is smaller and easier to bind to Ab. By modifying the nanobodies, researchers aim to achieve better therapeutic effects.

Moreover, an exciting new development in antibody-based therapies involves the use of nanobodies—small, single-domain antibodies derived from camelids or sharks. The current research approach is to target nanoantibodies to tau protein because of their small size, strong penetration of the blood-brain barrier, and ability to penetrate deep into the space between nerves to bind to the lesion site. Therefore, most researchers have tried to develop nanoantibodies targeting the tau protein. Studies have shown that nano-antibody is not easy to cause rejection in the human body due to its small structure, so it may have a reduced ARIA-E triggering rate, which makes nano-antibody drugs have excellent safety. The nanoantibody is stable in animal experiments, but its safety and efficacy still need to be further explored in human experiments.

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5. Conclusion

This article provides a comprehensive review of current and emerging monoclonal antibody treatments for Alzheimer's disease, specifically highlighting two clinically approved antibodies (Lecanemab and Donanemab) and several antibodies (Ponezumab, Semorinemab, and the UB-311 vaccine) currently in clinical trials. Most of these drugs target β-amyloid and tau protein and have achieved some effect in the clinical stage. However, most of these drugs are used to treat patients in the early stage of Alzheimer's disease, and they only slow down the rate of cognitive decline compared with traditional drugs but do not achieve the effect of improving cognitive performance. Although we try our best to avoid the risks of ARIA-E and ARIA-H, cerebral edema (ARIA-E) and microhemorrhage (ARIA-H) still occur in some patients during the treatment. This is the next step to avoid in future drug studies.

Facing the limitations of existing therapies, researchers have begun to explore a variety of emerging therapeutic strategies, including nanobody technology. Due to their small size, good stability, and superior blood-brain barrier penetration ability, nanoantibodies provide new possibilities for targeting other pathological markers such as tau protein. Future clinical studies should focus on optimizing dosing regimens, evaluating combination therapies, and enhancing antibody penetration to achieve improved clinical outcomes.

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