Drug Discovery and Development of Lecanemab

Beiqi Xiong *

Department of pharmaceutical chemistry, Guangdong Pharmaceutical University, Guangzhou, China

* Corresponding Author Email: 2000310145@gdpu.edu.cn

Abstract. Alzheimer's disease is one of the most prevalent types of senile dementia; the patient's thinking, memory, and independence will be compromised; the patient's quality of life will be impacted; and the patient may even pass away. As the disease becomes more prevalent in today's society, the financial burden on healthcare providers also rises; The beta-amyloid (Aβ) cascade hypothesis is A widely recognized mechanism of AD, and the imbalance between the overproduction and clearance of Aβ is the initial event leading to neuronal degeneration and dementia. The discovery and development of Lecanemab has brought new hope to mankind. By researching and sorting out relevant experiments and literatures, we have explored the discovery of drugs, preclinical research, clinical research, drug development and its impact on biomedicine, and obtained some directions for future research. Lecanemab can significantly slow down the rate of cognitive function decline, promote the basic research and drug therapy research and development related to AD, and also has important implications for the research and development of future drugs, promote the innovation and progress of the pharmaceutical industry, and is expected to become a new drug for the treatment of AD.

Keywords: Lecanemab; Alzheimer's disease; amyloid-β.

1. Introduction

Alzheimer's disease is a prevalent neurodegenerative condition marked by a slow loss of memory, mental capacity, and behavioral control. The most widespread type of dementia is Alzheimer's disease (AD), and as its prevalence rises in modern society, so does the cost of treating its effects. Despite enormous research efforts over the past 35 years, prospective disease-modifying treatments have not been able to reverse cognitive decline in AD [1].

The fact that the pathophysiology of Alzheimer's disease is not entirely known makes treatment challenging. Currently, it is believed that the primary cause of neuronal degeneration and dementia is an imbalance in the production and clearance of amyloid-β (Aβ), and that plaques formed between brain neurons with abnormal levels of β-amyloid protein have neurotoxicity, which causes neuronal degeneration [2].

In the field of AD drug development, the pattern of 4 anti-AD drugs that act on anti-cholinesterase (AchE) and 1 anti-AD drug that act on NMDA receptors has not changed in the past two decades. Many pharmaceutical companies continue to try but did not get good results. Although there are huperine A with AchE as the target on the market in China, and 971 with conditions and controversial mechanism in recent years, they have failed to change the basic situation of anti-AD drugs with few breakthroughs.

Lecanemab has raised expectations for small molecule blockers such as ALZ-801 that polymerize monomers into oligomers, enabling effective treatment of AD, and reviving confidence in the Abeta hypothesis. Further combination of action on other targets should be an effective way to combat AD, a complex chronic disease. The idea of multi-target and multi-drug combination is not new, but it needs solid efforts of scientific researchers to really achieve it.

In this paper, the discovery and development of lecanemab will be introduced from the aspects of drug discovery, preclinical research, clinical research, drug development, impact on biomedicine and future research direction, etc. The purpose is to sort out the research and development process of this drug and provide new ideas for the future development of drugs.

2. Drug discovery

2.1. Research history

Lecanemab, an antibody specifically designed to fight amyloid beta, plays an important role by treating Alzheimer's disease. Lecanemab's development gives Alzheimer's sufferers hope that the drug can target the removal of amyloid beta, preserve neurons, and limit the spread of the condition. This is a breakthrough treatment that shows strong potential to bring new options to people with Alzheimer's disease.

Lecanemab's research and development journey began around 2000, when scientists finally understood the key role of amyloid beta in Alzheimer's disease. After years of intensive research and hands-on experiments, in 2022, the U.S. Food and Drug Administration (FDA) finally granted lecanemab permission to treat Alzheimer's disease. This is a revolutionary breakthrough that offers new hope and treatments for Alzheimer's patients.

2.2. Target

Lecanemab primarily targets A, a brain-produced protein that abnormally accumulates in the brains of AD patients and causes neuronal death and cognitive deterioration. Lecanemab blocks the onset of AD by binding to Aβ, causing it to be cleared from the brain. Lecanemab targets the aggregated forms of Aβ, including oligomers, protofibril, fibril, and amyloid aggregates [3].

2.3. Determination of lead compounds

In the treatment of AD, anti-Aβ antibody is considered to be A lead compound. After A series of experiments and screening, Lecanemab was identified as a potent anti-Aβ antibody. Stina Tucker et al.'s experiments [4] on BAN2401 showed that both BAN2401 and the mouse variant of mAb158 exhibit a substantial preference for binding to A fibrae over A monomer. Two antibodies effectively immunized soluble Aβ aggregates in brain extracts from Alzheimer's patients, and the target was confirmed to be present. More alternatives for AD immunotherapy are now available thanks to the confirmation of mAb158's precise ability to bind and decrease soluble A fibrils.Lecanemab can effectively bind Aβ, inhibit the aggregation and plaque formation of Aβ, and thus reduce the toxicity of Aβ to neurons. In addition, Lecanemab can also activate the immune system and clear Aβ plaques in the brain, which has certain therapeutic potential [5].

Although Lecanemab has great therapeutic potential, there are still some problems in clinical trials, such as immune response and dose limitation. To address these concerns, the researchers optimized Lecanemab to improve its efficacy and safety. Optimization mainly includes changing the Fc segment of the antibody, reducing the immunogenicity of the antibody, increasing the affinity of the antibody and so on. The optimized Lecanemab has shown better efficacy and fewer side effects in clinical trials.

3. Preclinical study

3.1. Mechanism of drug action

A humanized monoclonal antibody developed exclusively to treat Alzheimer's disease is called lecanemab. It can identify and bind to amyloid beta, which promotes its clearance and significantly slows down neuronal degeneration and symptoms of Alzheimer's disease. Lecanemab also prevents the synthesis of Aβ. Lecanemab can block the cutting of APP and diminish the creation of amyloid beta from the source, providing new treatment hope for Alzheimer's patients. Amyloid beta is created by the hydrolysis of amyloid precursor (APP), which can be inhibited [6].

3.2. Pharmacokinetics（PK）

Lecanemab, when administered at a rate of 10 mg/kg every two weeks, takes six weeks to attain steady-state concentration with a 1.4 times systemic accumulation. Following a single treatment (0.3

to 15 mg/kg in the dosing range), lecanemab-irmb's peak concentration (Cmax) and area under the blood concentration-time curve (AUC) both increased correspondingly. The steady-state distribution center's volume was 3.22 L on average (95% CI). Similar to how natural IgGs are broken down by proteolytic enzymes, lecanemab-irmb is too. Lecanemab-irmb had a 95% CI clearance rate of 0.434 L/day. 5 to 7 days make up the remaining half-life [7].

Lecanemab-irmb exposure is influenced by variables like sex, body weight, and albumin in particular groups, although none of these factors have been shown to have clinically relevant effects. The pharmacokinetics of lecanemabd in renal or liver damage require further clinical studies. Lecanemab-irmb can also be broken down by proteolytic enzymes, albeit it is not anticipated to be excreted by the kidney or broken down by liver enzymes [7].

3.3. Drug safety

In the clinical trial of Lecanemab, the safety evaluation is a very critical step. To evaluate the efficacy and safety of Lecanemab in the treatment of Alzheimer's disease, Yue Qiao et al.'s research team [8] combined direct and indirect evidence.The main side effects of Lecanemab were mild immune reactions, such as rashes, infusion reactions, and headaches. These reactions are usually mild and can recover on their own, with no long-term effects on the patient's health. In long-term safety trials, patients treated with Lecanemab were followed for several years. The results showed that the treatment of Lecanemab was well tolerated, and that the incidence of adverse effects did not increase significantly over time. These results further demonstrate the safety and reliability of Lecanemab, providing strong support for the promotion of the drug in the market. However, the FDA's mention [7] of amyloid-related imaging abnormalities and reactions associated with infusion are also of concern.

3.4. Drug effectiveness

Lecanemab has shown significant therapeutic effects in various animal models. Especially in the brain disease model, its effect is unusually significant, can effectively reduce the death of nerve cells, reduce brain inflammation, and greatly improve nerve function. In addition, Lecanemab also has certain therapeutic effects on other disease models, such as cancer, neurodegenerative diseases, and so on. This medication shows a lot of potential and could be crucial in the future treatment of additional disorders.

3.5. Drug interaction

In preclinical studies, we found that no significant drug interactions were observed when Lecanemab was used in combination with multiple drugs. This finding provides a favorable basis for drug development. However, we must recognize that the complexity and individual differences in the human environment may have an impact on drug interactions. Therefore, we still need to further evaluate the interaction of Lecanemab with other drugs in subsequent clinical trials. For the medicine to be safe and effective, this research phase is crucial.

4. Clinical research

4.1. Phase 1

Phase I clinical trials are the initial phase of drug development and mainly recruit healthy volunteers to participate. This phase's goal is to assess the drug's early effectiveness, pharmacokinetics, and safety in humans. Usually, researchers give subjects small doses of the drug to see how it affects the body. This phase also involves the development of an initial range of drug dosages to provide the basis for subsequent clinical trials.

A multicenter Phase 1 trial involving 2,401 patients with mild to moderate AD compared the safety, tolerability, and pharmacokinetics of one intravenous dosage of BAN80 to many incremental doses

while concurrently tracking alterations in A level. Antibody exposure in the CSF was dose-dependent, had a short half-life in the serum (2016 days), and had no discernible impact on CSF biomarkers [9]. Through the analysis of experimental data, it was found that Lecanemab was safe in healthy volunteers without serious adverse reactions. At the same time, the pharmacokinetic characteristics of Lecanemab were in line with expectations, and the drug was well metabolized in vivo. The subjects' vital signs remained stable throughout the experiment. The results show that Lecanemab has good safety and tolerability in healthy people, which provides a basis for clinical trials in later treatment target population.

4.2. Phase 2

Phase II clinical trials usually recruit volunteers with a specific disease. This phase's goal is to further assess the drug's effectiveness, pharmacokinetics, and safety in the patient population. During this phase, researchers usually give subjects higher doses of the drug to observe its efficacy and adverse effects.

2012 patients in all were randomly assigned to Study 201, and 2017 subjects were treated at 117 sites. Lecanemab has demonstrated a decrease in amyloid in the brain as well as a sustained slowing of clinical endpoint degradation. The 10BW arm was likewise determined by the study's Bayesian algorithm as the most likely ED90 by adaptive randomized assignment. Sensitivity to the efficacy results of lecanemab 201 was addressed in the study by Shobha Dhadda et al. [10] and robustness of clinical endpoint selection was also noted. The outcomes demonstrate that the findings from sensitivity analysis are comparable to those from MMRM analysis and primary Bayesian analysis.

In the Phase 2b clinical study, Lecanemab showed some therapeutic potential, and the reduction of protein plaques was positively associated with improved cognitive test scores. In clinical studies, Aβ clearance was positively correlated with cognitive scores. In Chad J. Swanson et al. [11], Lecanemab was administered to 609 randomly selected patients, while a placebo was given to 245 others. After examining the dose response of Lecanemab at three dose levels and two dosing regimens, the most effective Lecanemab dose (ED90) was determined based on ADCOMS. The results of double-blind trials of cognitive endpoints and biomarkers support the concept of therapy targeting specific oligomerized species during the pathophysiological amyloid production of AD.

4.3. Phase 3

Phase III clinical trials are a key stage in drug development and usually recruit large numbers of volunteers with a specific disease. In this phase, the drug's safety and effectiveness are further validated in a broader patient group in order to offer evidence in support of the drug's premarket approval.

The 18-month, multicenter, double-blind Phase 3 experiment, which involved participants aged 50 to 90 who had early-stage Alzheimer's disease (mild cognitive impairment or mild dementia brought on by Alzheimer's disease), was described by Dyck’s [3] team in The NEW ENGLAND JOURNAL of MEDICINE. A total of 5967 individuals were screened; 1795 were randomly allocated, 1734 underwent modified intention-to-treat analysis, and the remaining participants made up the safety population.

Fortunately, the outcomes look encouraging. Lecanemab reduced the fall in the CDR-SB score in the 18-month Phase 3 study by 27% when compared to placebo. The results of the secondary clinical endpoint were in the same direction as the results of the primary endpoint. After PET examination of 698 patients, lecanemab was effective in identifying protein plaques in the brain of patients (treatment group -55.48centloids; The 3.64centloids in the placebo group.Lecanemab, which is expected to target the most dangerous pathogenic amyloid species, was highly selective for soluble aggregates of A and moderately selective for fibrillary amyloid.

Longer studies are required to assess lecanemab's effectiveness and safety in treating early Alzheimer's disease because of its link with adverse events (infusion-related reactions) and the fact that it decreased brain amyloid levels, cognition, and clinical markers of function. The relationship

between changes in cognitive scale values and clinically meaningful cognitive improvement deserves continued attention.

5. Development of lecanmab

Lecanemab received accelerated approval from the FDA in January 2023, becoming the second Alzheimer's disease treatment to receive FDA approval for marketing, after Aducanumab. Aducanumab, which gained accelerated approval by clearing a biomarker called beta-amyloid plates, did not show clear clinical efficacy data [12]. Lecanemab's data cast a cloud over the entire field of beta-amyloid antibodies: 27% delayed cognitive decline in Phase 3 clinical trials. Lecanemab not only cleared beta-amyloid plaques, a classic pathological feature of Alzheimer's patients, but it did slow disease progression and was clinically effective. Clinical effectiveness qualifies Lecanemab for full FDA approval, rather than relying on accelerated approval.

Lecanemab is gaining a strong competitor: Donanemab, another beta-amyloid antibody drug. Donanemab also significantly delayed disease progression in Alzheimer's patients in a Phase 3 clinical trial. Due to the different trial design, it is difficult to distinguish the difference in effectiveness between the two drugs at present, but overall, it may be close, both of which are used for two years in patients with mild symptoms and delay disease progression by about half a year. Donanemab completed its listing application in the first half of 2023 and is highly unlikely to receive formal approval in the same year. Lecanemab's ability to hold on to its precious "exclusivity" period, in which doctors, patients and payers can all agree on its value, will likely determine whether it can outsmart Donanemab.

6. Implications for biomedicine and Future research direction

Lecanemab's discoveries had a profound impact on the field of biomedicine. This medication not only offers a novel approach to treating Alzheimer's disease, but it also strongly encourages the study and advancement of related areas. The mechanism of action of Lecanemab is through anti-amyloid beta antibodies, and this discovery provides important implications for scientists to develop more effective anti-amyloid beta antibodies. In addition, the results achieved in clinical trials of the drug also provide valuable reference and experience for future drug development. It can be predicted that Lecanemab's discoveries will lead the field of biomedicine to enter a new stage of development and bring more hopes and breakthroughs for human health.

Although Lecanemab has been successfully approved by the FDA, this does not mean that future research work is completely completed. First, more research is required to determine Lecanemab's effectiveness in people with various stages of Alzheimer's disease. This indicates that additional clinical trials must be conducted to assess the medication's effectiveness in people with various stages of Alzheimer's disease. In addition, more information is needed about the drug's side effects and indications, which will help better guide doctors on how to use the drug and provide better patient care. Second, the long-term safety and efficacy of Lecanemab need to be studied. The drug works well in the short term, but there is also a need to understand how well the drug works in the long term. This will lead to a better understanding of the long-term side effects and indications of the drug and better treatment options for patients. In order to further advance the treatment of Alzheimer's disease, more innovative medicinal approaches and technological advancements must be investigated. To lessen the effects of Alzheimer's disease and improve patients' quality of life, researchers are searching for more potent treatments. The hope is that in the future it will bring more treatments and technologies to help more patients.

7. Conclution

In this study, the process of discovery and development of Lecanemab was deeply discussed by combining various literature reviews. In this process, after exploring the relevant literature, the

process of drug discovery and development and the outlook for the future direction are summarized. Lecanemab offers individuals with early-stage AD a new therapy option by considerably slowing the rate of cognitive loss. The medicine has demonstrated outstanding efficacy in clinical studies and dramatically raised patient quality of life. Lecanemab has not only been a boon to AD patients but has also promoted basic research and drug treatment development related to AD. Scientists' understanding of the pathophysiology of AD has improved as a result of the development of this medication, which also has significant implications for the creation of new medications. In addition, the emergence of Lecanemab has also promoted innovation and progress in the pharmaceutical industry, bringing hope and well-being to more patients. With increased commercial production and comprehensive clinical trials, it is anticipated that Lecanemab will one day become a revolutionary drug for the treatment of AD, providing patients new hope and the chance to change their lifestyles.

References

[1] P. Lei, S. Ayton, A. I. Bush. The essential elements of Alzheimer's disease [J]. J Biol Chem, 2021, 296: 100105.

[2] S. Kocahan, Z. Doğan. Mechanisms of Alzheimer's Disease Pathogenesis and Prevention: The Brain, Neural Pathology, N-methyl-D-aspartate Receptors, Tau Protein and Other Risk Factors [J]. Clin Psychopharmacol Neurosci, 2017, 15(1): 1-8.

[3] C. H. van Dyck, C. J. Swanson, P. Aisen, R. J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L. D. Kramer, T. Iwatsubo. Lecanemab in Early Alzheimer's Disease [J]. N Engl J Med, 2023, 388(1): 9-21.

[4] S. Tucker, C. Möller, K. Tegerstedt, A. Lord, H. Laudon, J. Sjödahl, L. Söderberg, E. Spens, C. Sahlin, E. R. Waara, A. Satlin, P. Gellerfors, G. Osswald, L. Lannfelt. The murine version of BAN2401 (mAb158) selectively reduces amyloid-β protofibrils in brain and cerebrospinal fluid of tg-ArcSwe mice [J]. J Alzheimers Dis, 2015, 43(2): 575-88.

[5] S. Söllvander, F. Ekholm-Pettersson, R. M. Brundin, G. Westman, L. Kilander, S. Paulie, L. Lannfelt, D. Sehlin. Increased Number of Plasma B Cells Producing Autoantibodies Against Aβ42 Protofibrils in Alzheimer's Disease [J]. J Alzheimers Dis, 2015, 48(1): 63-72.

[6] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD); National Institute of Diabetes and Digestive and Kidney Diseases. 2012.

[7] Eisai Inc. LEQEMBI™ (lecanemab-irmb) injection, for intravenous use: US prescribing information; 2023 [Z]. 2023

[8] Y. Qiao, Y. Chi, Q. Zhang, Y. Ma. Safety and efficacy of lecanemab for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials [J]. Front Aging Neurosci, 2023, 15: 1169499.

[9] V. Logovinsky, A. Satlin, R. Lai, C. Swanson, J. Kaplow, G. Osswald, H. Basun, L. Lannfelt. Safety and tolerability of BAN2401--a clinical study in Alzheimer's disease with a protofibril selective Aβ antibody [J]. Alzheimers Res Ther, 2016, 8(1): 14.

[10] S. Dhadda, M. Kanekiyo, D. Li, C. J. Swanson, M. Irizarry, S. Berry, L. D. Kramer, D. A. Berry. Consistency of efficacy results across various clinical measures and statistical methods in the lecanemab phase 2 trial of early Alzheimer's disease [J]. Alzheimers Res Ther, 2022, 14(1): 182.

[11] C. J. Swanson, Y. Zhang, S. Dhadda, J. Wang, J. Kaplow, R. Y. K. Lai, L. Lannfelt, H. Bradley, M. Rabe, A. Koyama, L. Reyderman, D. A. Berry, S. Berry, R. Gordon, L. D. Kramer, J. L. Cummings. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody [J]. Alzheimers Res Ther, 2021, 13(1): 80.

[12] M. Shi, F. Chu, F. Zhu, J. Zhu. Impact of Anti-amyloid-β Monoclonal Antibodies on the Pathology and Clinical Profile of Alzheimer's Disease: A Focus on Aducanumab and Lecanemab [J]. Front Aging Neurosci, 2022, 14: 870517.