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Exploring Lecanemab: Mechanisms, Efficacy, and Clinical Implications in Alzheimer's Disease Management

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Abstract. Lecanemab, with accelerated approval from the FDA, becomes a notable and promising drug to fight against Alzheimer's disease (AD). As one monoclonal antibody, it is reported that lecanemab can reduce cognitive decline caused by AD by reducing amyloid-beta in patients. However, some concerns, uncertainties and limitations of Lecanemab in clinical trials have also been brought out. This study analyses the existing methods to cure AD and researches in clinical phases of lecanemab and relevant detailed information. This article aims to provide a relevant view of key aspects of lecanemab's performance, including its mechanisms, effects, safety, limitations and tips. Thus, this study shows an updated summary for those who want to be exposed to the current situations of applications of Lecanemab. The nature of AD remains complex to us nowadays, so further fundamental research concerning the causes and mechanisms of AD. For those drugs targeting AD, many aspects involving itself and its usage still need to be investigated.

Keywords: Alzheimer's disease; lecanemab; clinical progress.

1. Introduction

The features of AD include neurocognitive disability, tau protein deposits, and Deposits of beta-amyloid peptides [1]. The Alzheimer's Association reports that about one-third of the elderly population died because of AD or similar diseases [2]. The number of global AD cases is predicted to grow three times over by 2050, exceeding 100 million cases worldwide [2]. Evidence from research firmly revealed that the monoclonal antibodies have significant potential to improve the cognitive decline related to AD by precisely targeting amyloid-beta and tau pathological processes [3]. Overall, the application of monoclonal antibodies in treating AD marks a significant milestone, providing a specialized and focused method to deal with the core pathological mechanisms [3]. The drug lecanemab, one Aβ monoclonal antibody, have shown a positive and notable reduction in cognitive and functional decline. Considering this context, the further research of Lecanemab would be important.

Although the exact causes of AD have not been fully understood, it is widely believed that the accumulation of Aβ is a key contributor to development of AD [4]. Lecanemab is designed to slow down the progress of AD and enhance patients' cognitive abilities by targeting Aβ plaques, one fundamental feature of AD [5].

This study aims to thoroughly analyze the preclinical and clinical research outcomes of Lecanemab, discover its ability in the treatment of AD, and Investigate the likely difficulties in its actual clinical usage. This study will not only further enhance the comprehensive knowledge of how AD is treated by Lecanemab, but will also play a crucial role in guiding the future creation of drugs for AD and the formulation of new treatment strategies.

This review will highlight the functional mechanism of Lecanemab, its clinical trial development, safety evaluation and potential treatment methods in the future. Thus, a more comprehensive overview and illustration will be provided to reveal the current performance and future usage prospects of lecanemab, assessing its potential value in curing patients in the early stage of AD. All readers can get updated information about this drug and be more familiar with its current situation.

Decision-making supports will also be offered for professional clinicians and researchers to serve as recommendations to be considered in clinical trials and further studies.

2. General Review of Existing Therapies for AD

Today people don't have perfect therapy to cure AD completely. It is reported that using some existing methods to cure AD will still get a high failure rate [6]. This happens mainly because the pathologic causes of AD are quite complex, the comprehension of the relationship between the mechanism of the development of AD and the decreasing number of neurons afterward is incomplete, and current available agents are potentially ineffective [6]. By 2022, the therapies for patients with AD is still complicated owing to the disease's complexity [6]. As shown in table 1, people only have treatments like cholinesterase inhibitors, memantine, or a combination of these drugs approved for AD [6]. Besides, a large amount of drug candidates have failed to pass Phase 3 tests since they failed to meet the required efficacy request [6].

Table 1. Summary of different types of therapy for AD (ND: not describe)

Type of therapy	Cognitive functions	Attention	Memory	Aβ plaques	Proinflammatory progression response of ad	Side effects
Cholinesterase inhibitors	↑	↑	↑			Insomnia, gastrointestinal symptoms (nausea, loss of appetite, diarrhea), muscle cramping and weakness
Memantine	↑		↑			Confusion,aniety
Aducanumab	↑			Removal, Disturbing accumulation		Micro-bleeds, swelling in the brain, dizziness headaches nausea
Antidepressants						Citalopram: risk of qt prolongation
Vitamin e	↑					Overdosage: fatigue, Gastrointestinal cramps, Diarrhea
Melatonin				Prevent Accumulation	↓	ND
Curcumin	↑			Prevent Accumulation		ND
Ginkgo biloba	↑			↓		ND
Saffron	↑		↑			ND
Ashwaganda				↓toxicity		ND
Physical activities	↑					ND
Social activities	↑					ND
Music therapy	↑		↑			ND
Anti-inflammatory treatment	↑			↓pathology		ND
Gut microbiota alterations				Stopping Development		ND

Another study examined the Methodic quality of systematic reviews (SRs) on treatments for AD, along with their potentially relevant factors [7]. Carefully conducted SRs can tell whether the treatment strategies are effective for AD [7]. It appraises the methodological quality of a sample of 102 SRs on AD treatments published between 2014 and 2021 [7]. Within the group, merely 4 (3.9%) SRs achieved a high overall quality rating, with 14 (13.7%) at a moderate level, 48 (47.1%) as low overall quality, and 36 (35.3%) of the poorest, critically low overall quality [9]. Results from the research suggest that most SRs on AD treatments have a low or critically low level of Methodological quality [7]. Thus, more therapies and treatments still need to be developed.

3. Drug profile

3.1. Effectiveness & Safety Concerns

Lecanemab shows positive effects in slowing down the cognitive decline in patients with early AD [8]. The efficiency and reliability of Lecanemab have been tested in many kinds of clinical tests [8]. One phase 2 study with early AD with hundreds of patients involved (Lecanemab group 609; placebo group 245) revealed that Lecanemab can dramaticallly reduced Aβ plaque burden in patients [8].

Possible mechanisms of anti-amyloid antibodies like Lecanemab: (1) During the preclinical stage, animals are given Injections of anti-amyloid antibodies, while patients with AD are given these antibodies via infusion in clinical studies. (2) Both the body and the brain are targeted by antibodies, removing amyloid effectively. (3) Antibodies are able to eliminate amyloid peptides before they assemble into characteristic plaques. (4) These antibodies can interact with established plaques. (5) Immunoglobulins can prompt immune cells for removing amyloid. The illustration was produced with BioRender.com [8]

Additionally, patients showed a significant enhancement from the aspects of their cognitive skills and daily living activities. Their outcomes This outcome aligns with primary endpoints, indicating the Lecanemab's potential to boost cognitive and functional abilities caused by AD [9]. Another team conducted an SR and meta-analysis of the cognitive effectiveness and safety of lecanemab in subjects with AD. [9] Methods: A search was performed in databases including PubMed, Embase, Web of Science, and Cochrane, seeking data concerning randomized controlled trials that investigated lecanemab's efficacy [9]. Results: A total of four randomized controlled trials were included, involving 3,108 AD patients (1,695 in the lecanemab group and 1,413 in the placebo group) to synthesize evidence. The two groups shared alike characteristics of the participants in all measures with the exception of the ApoE 4 genotype and the lecanemab group's superior MMSE scores. Findings suggest that lecanemab has a positive impact on maintaining or decelerating the decline in CDR-SB scores in patients with early AD [9] The CDR-SB score is a tool for quantifying cognitive decline, with elevated scores denoting more substantial cognitive decline [9].

Their analysis found that lecanemab demonstrated significant positive statistical efficacy with respect to cognition, function, and behavior in patients with early AD [8]. The consistent outcomes across the studies affirm the dependability of the findings. Overall, lecanemab has shown a decrease in amyloid biomarkers in the early stages of AD [8]. It is also associated with relatively smaller decrease in cognitive and functional performance compared to the placebo group at the 18-month point [8]. Still, this research underscores that the advantages of lecanemab should be considered in light of its possible side effects, particularly ARIA, characterized by various levels of cerebral bleeding or fluid buildup [10]. Additional monitoring is required to assess the potential risks of ARIA for patients receiving anticoagulation treatment, potentially leading to the exclusion of this group [8]. Thus, additional trials with longer time are necessary to prove the effectiveness and safety of lecanemab for patients with early AD.

Another team conducted one complete review and meta-analysis to examine the cognitive performance and safety of lecanemab treatment in AD cases [9]. Their research indicates that Lecanemab has a significant beneficial influence on the cognition, function, and behavior of patients

suffering from early AD, while the full clinical importance is yet to be completely confirmed [9]. In general, this team conducted research based on the publications in PubMed, Embase, Web of Science, and Cochrane databases published before February 2023, focusing their attention on randomized controlled trials that used Lecanemab to cure cognitive decline in patients with AD [9]. The evidence of this synthesis included four randomized controlled trials, comprising 1,695 patients with AD in the lecanemab groups and 1,413 in the placebo groups [9]. It is reported that lecanemab was beneficial in stabilizing or slowing down the decrease in CDR-SB and amyloid burden on PET [9]. However, this article also emphasized some limitations by now. The widespread use of their research outcomes would be narrowed by the small number of existing trials and patients involved [9]. This team mainly observes the differences in cognitive function in clinical results. But, many of the measurement tools to test the benefits of lecanemab are largely outdated and have been identified as unreliable [9]. Taking the MMSE as an example, it has been questioned for its dependability owing to its non-linear relationship with the disease's timeline, especially in the pre-moderate dementia stage [9]. Moreover, the actual meaning of the changes in the CDR-SB score is in doubt, since the relationship between the time change and risk of random effects has not been properly evaluated [9]. These results provide valuable insights into the potential effectiveness of lecanemab as a therapeutic intervention for addressing cognitive impairment in this patient population. [9]

Overall, this study indicates that lecanemab may have the ability to slow down cognitive decline in individuals with early AD, yet its effectiveness in functional impairment, behavioral changes, and systemic symptoms with severe AD is doubtful [9].

Thus, on the one hand, this drug introduces a new approach to curing dementia. Lecanemab has been shown to significantly reduce the rate of cognitive decline in phase III study and is effective in lowering Aβ accumulation in individuals suffering from early AD. Thus, this drug might not only play a role in slowing the worsening of cognitive decline but also in boosting the well-being of patients with AD and their relatives.

Although there is no strong evidence to suggest a significant difference in the occurrence of TEAEs (Treatment-Emergent Adverse Events), the meta-analysis has raised substantial safety concerns regarding the increased risk of ARIA-E (Amyloid-Related Imaging Abnormalities - Edema) and ARIA-H (Amyloid-Related Imaging Abnormalities - Hemorrhage) associated with Lecanemab at a dose of 10 mg/kg administered biweekly, compared to placebo [9]. These findings, particularly the heightened risk of ARIA-H, underscore the importance of careful consideration and monitoring of the safety profile of Lecanemab in clinical practice [9].

3.2. Limitations

Lecanemab received accelerated approval from FDA for its effectiveness in clearing amyloid from the brain. Nevertheless, the connection between the achievement of amyloid-negative status and the reduction in cognitive decline has not been clearly identified, with the inconsistent or irregular effect of anti-amyloid therapies on cognitive decline [10]. In addition, some participants in the placebo group in the clinical studies researching Lecanemab had achieved amyloid-negative status [10]. These phenomena highlight the complex nature of AD and underscores our incomplete understanding of amyloid's role in AD with its partially understood effect on clinical outcomes [10]. Moreover, while the MCID data and some ideas from clinical experts represent that the usage of Lecanemab has led to a notable statistical reduction in the speed of cognitive decline, such improvement might not be regarded as clinically meaningful [10].

A Markov model was created to evaluate Lecanemab's cost-effectiveness over the lifetime [10]. The key assumptions of this model involve the function of lecanemab in delaying the disease progression when a patient has mild AD [10]. Once the patient's condition achieves moderate AD, the Lecanemab treatment is stopped [10]. The outcome shows that from the perspective of the health care system and modified society, the yearly price of lecanemab at $26,500 exceeds standard cost-effectiveness thresholds [10].

4. Recommendations

Side effects can be associated with Lecanemab treatment, like myloid-related imaging abnormalities (ARIA) and reactions during infusion, with most of these cases are without symptoms, a few can be severe, and very occasionally, they can be fatal [11]. Thus, appropriate Use Recommendations (AURs) relying on clinical trial results and AD-related research is needed to guide clinicians to apply Lecanemab in the safest and most effective way [11]. The study also emphasized that It is essential for clinicians and institutions to be prepared before using lecanemab, and there should be agreements in place for managing any serious events that may happen [11]. Meanwhile, open communication between physicians and candidates for or undergoing lecanemab therapy is a crucial factor in good clinical practicels [11]. Patients and their care partners should have a clear view of the expected benefits, the potential harms, and monitoring needs for treatment with lecanemab involved [11]. The development of trust via culture-specific communication between clinicians and patients is crucial for the success of using lecanemab effectively [11].

5. Conclusion

This study discussed the comparisons among various methods for early AD, and focus the attention on several perspectives of lenanemab's performance in its clinical trials and testing. By analyzing this information from different aspects, we not only get a general idea about the development of the usage of lecanemab when it went to the market and relevant research progress on it. We can notice the complexity of the treatment of AD in real therapy and the necessity of further in-depth study for both the disease and related treatments. By referring to this study, we can get some critical ideas about the new-approved drug lecanemab. This study will not only provide summary for those who are interested in this drug and relevant treatments but also reveal some of the problems and arguments along the way. Thus, further research and possible questions that are valuable would be conducted based on the situations that are shown in this article. Meanwhile, owing to the word restrictions, we can only focus the attention on some key aspects of lecanemab's clinical testing. So, some detailed content can't be shown in this article, and these key points might not be deep enough compared with the monographic studies. Moreover, owing to the restricted data and the subjectivity of some research, this article can only give parts of the main outcomes and ideas in the research fields. Based on this article, more research could be conducted to give a wider or deeper view of the treatment of AD or new information for the drug lecanemab.

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