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Lecanemab: A Breakthrough in Alzheimer's Disease Treatment

Vankodoth Sireesha[1]; N. Chaitanya[2]; Meghana. Ch[3]; K. Megana[4]
[1,2,3,4]Department of Pharm D, CMR College of pharmacy Hyderabad, Telangana

Abstract:- Lecanemab is a groundbreaking treatment for Alzheimer's disease, showing significant promise in slowing cognitive decline in patients with early-stage disease. Lecanemab is the most recent monoclonal antibody to target beta-amyloid and is licensed only for the treatment of mild cognitive impairment or mild dementia associated with Alzheimer's disease. Lecanemab represents a fresh approach to targeting the pathophysiology underlying the condition, and the encouraging outcomes of the Phase 3 trial provide hope to patients and their families. Although more research is need to determine lecanemab's safety and efficacy, the results of the Phase 3 trial suggest that it could greatly improve AD treatment options. This review explores the mechanism of action, clinical trial data, potential impacts, and future directions for this monoclonal antibody therapy.

Keywords:- *Alzheimer's Disease; Amyloid-Beta; Amyloid-Related Imaging Abnormalities (ARIA); CLARITY AD Trial; Cognitive Decline; Disease-Modifying Therapies; Early-Stage Alzheimer's; Lecanemab; Monoclonal Antibody Therapy; Neurodegenerative Diseases.*

I. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting millions worldwide, characterized by memory loss, cognitive dysfunction, and personality changes [3]. The development of amyloid-beta plaques in the brain has been one of the key pathological markers of the disease [3]. After years of research with minimal success, recent breakthroughs, particularly with monoclonal antibodies like Lecanemab, have shown the potential to modify the course of the disease, offering hope for slowing its progression [4]. Lecanemab is the most recent monoclonal antibody to target beta-amyloid and is licensed only for the treatment of mild cognitive impairment or mild dementia associated with Alzheimer's disease.

II. MECHANISM OF ACTION

Lecanemab is a monoclonal antibody that targets amyloid-beta protofibrils, which are soluble forms of amyloid that aggregate and form plaques in the brain [2]. By binding to these protofibrils, Lecanemab helps clear them from the brain, reducing the burden of amyloid plaques, which are thought to contribute to the cognitive decline seen in Alzheimer's patients [2,5].

Lecanemab is administered as a one-hour intravenous (IV) infusion every two weeks at a dose of 10 mg/kg. The Steady-state concentrations of lecanemab were reached after six weeks when 10 mg/kg of lecanemab was administered every two weeks. Systemic accumulation was 1.4-fold. The peak concentration (Cmax) and area under the plasma concentration versus time curve (AUC) of lecanemab increased dose proportionally following a single dose ranging from 0.3 to 15 mg/kg. The mean value (95% CI) for the central volume of distribution at steady-state is 3.2.

III. CLINICAL TRIALS

The approval of Lecanemab was primarily based on results from the CLARITY AD trial, a phase III study that involved 1,795 participants with early Alzheimer's disease [1]. Over an 18-month period, patients receiving Lecanemab showed a 27% slower decline in cognitive function compared to those receiving a placebo [1,4]. This was measured using clinical assessments such as the Clinical Dementia Rating-Sum of Boxes (CDR-SB) scale [5]. The treatment also resulted in a significant reduction of amyloid plaques in the brain, confirmed by PET scans [5,6].

However, Lecanemab is not without risks. Some patients in the trial experienced adverse effects, including amyloid-related imaging abnormalities (ARIA), which can cause brain swelling or bleeding [7]. This is a common risk associated with amyloid-targeting therapies, and careful monitoring is necessary for patients undergoing treatment [7].

IV. IMPACTS OF LECANEMAB

The approval of Lecanemab marks a significant step forward in Alzheimer's treatment. It is one of the few drugs that directly targets the disease's pathology, rather than just addressing symptoms [2]. This represents a shift toward disease-modifying therapies that aim to alter the course of Alzheimer's progression [8].

For patients and families, Lecanemab offers hope for maintaining cognitive function for longer, potentially preserving quality of life [9]. Additionally, the drug's success could pave the way for further advancements in the field of neurodegenerative diseases, encouraging more research into amyloid-targeting therapies and other disease-modifying treatments [9].

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The most common side effect (26.4% of participants vs. 7.4% in the placebo group) of the treatment is an infusion-related reaction, which may include transient symptoms, such as flushing, chills, fever, rash, and body aches. The majority (96%) of these reactions were mild to moderate, and 75% happened after the first dose. Lecanemab is degraded by proteolytic enzymes in the same manner as endogenous IgGs. The terminal half-life is 5 to 7 days.

V. EFFICACY AND SAFETY

An 18-month experiment was conducted by H. van Dyck and his team (Ouzzani et al., 2016) to assess the benefits of lecanemab. Lecanemab's clinical decline, the primary endpoint, was noted in CDR-SB (Clinical Dementia Rating Scale Sum Boxes) (difference, −.45; 95% confidence interval, −.67 to −.23; no significance level). Regarding the secondary outcome, there was a clinical decrease in the amyloid load on PET, ADAS-cog14 score, ADCOMS, and ADCS-ADL-MCI, with differences of −59.12 centroids, −1.44, −0.050, and 2, among others.[10]

In a 12-month experiment, Swanson et al. (2018) and his colleagues assessed the benefits of lecanemab. The primary endpoint at 12 months failed to meet the 80% criteria for the primary outcome, with a 64% likelihood that it was better than the placebo by 25% on ADCOMS.[11]

According to H. vanDyck (Ouzzani et al., 2016), the most frequent adverse event following a single dose is due to infusion (26.4% with lecanemab vs. 7.4% with placebo). Participants who received lecanemab exhibited a greater incidence of amyloid-related imaging abnormalities (ARIA)-H (17.3% vs. 9.0%) and ARIA-E (12.6% vs. 1.7%).

Both the lecanemab and placebo groups had modest rates of death (0.7% and 0.8%, respectively), and none of the deaths were thought to be caused by the medication. In both groups, the overall incidence of adverse events was comparable.Angina pectoris, atrial fibrillation, syncope, infusion-related responses, and ARIA-E were the most frequently reported major adverse events associated with lecanemab.

Early in AD, lecanemab exhibits encouraging effects (Ouzzani et al., 2016; Swanson et al., 2018). However, using it can have some significant negative effects as well (Swanson et al., 2021). Consequently, care should be used before using lecanemab. Individuals suffering with Amyloid-related imaging abnormalities (ARIAs) exhibit significant impairments to their gray and white matter. These abnormalities are commonly experienced by those receiving these therapy, and they suggest a persistent brain injury.[12]

To evaluate the deleterious consequences, FDG-PET imaging should be used both before and after antibody therapy (Høilund-Carlsen et al., 2023). [13]

VI. CHALLENGES AND FUTURE DIRECTIONS

While Lecanemab is a promising breakthrough, several challenges remain. The drug is most effective in the early stages of Alzheimer's, meaning early diagnosis is crucial [14]. However, diagnosing Alzheimer's at an early stage can be difficult, as symptoms are often subtle. Improved diagnostic tools, including biomarkers and advanced imaging techniques, will be critical in identifying candidates for treatment [14,15].

Moreover, the cost of Lecanemab is a concern, as it is expected to be expensive, potentially limiting access for some patients [16]. Insurance coverage and healthcare system preparedness will play key roles in determining the reach of this therapy [16].

Looking ahead, the success of Lecanemab raises questions about its long-term effectiveness. Continued research is needed to assess the drug's impact beyond the 18-month trial period and to determine whether it can prevent or delay more severe stages of Alzheimer's disease [17]. Additionally, combination therapies targeting multiple aspects of Alzheimer's pathology, including tau proteins and neuroinflammation, may further enhance treatment outcomes [18,19].

VII. RECOMMENDATIONS

There should be no signs of cerebrovascular illness in patients using lecanemab. Lecanemab shouldn't be administered to patients who are on anticoagulants or who require thrombolytic therapy for an ischemic stroke. Every other week, the therapy is given intravenously without titrating. A baseline MRI scan is advised, as well as one prior to the fifth, seventh, and fourteenth infusions and at 52 weeks for patients who have had an ARIA. If signs of ARIA appear, more MRIs are required. Because infusion reactions are frequent, anti-inflammatory medication precautions may be necessary.[20]

VIII. CONCLUSION

Lecanemab represents a fresh approach to treating the underlying pathology causing the sickness. Although more research is need to determine lecanemab's safety and efficacy, the results of the Phase 3 trial suggest that it may considerably improve AD treatment options (Rodriquez, 2023). Based on the results of its Phase 2 clinical trial, the FDA approved this medication through an expedited pathway (Food and Drug Administration (FDA) (2023); Rodriquez, 2023). The FDA approved anti-amyloid antibodies based on HOSSAIN ET AL. 9 of 10 the elimination of amyloid plaques found on PET scans.

Lecanemab is a major advancement in Alzheimer's disease treatment, offering hope for slowing the progression of cognitive decline. While not without risks, its approval signals a new era of disease-modifying therapies in the battle against Alzheimer's. As research continues, Lecanemab may

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lead to further breakthroughs, improving the lives of millions affected by this devastating disease.

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