Teli and Dhande
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COMMENTARY

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Advancing Alzheimer's care: a novel therapy with lecanemab

Advait Teli[1] and Priti Dhande[1*]

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects the patient's quality of life. The current regime of drugs only halts the symptoms of the disease, and the underlying pathology remains untouched; thus, there is progressive deterioration due to the intact pathology. Various drugs are being researched to address the complex neuropathology of AD. The FDA has approved lecanemab, which has shown considerable efficacy in reducing Aβ plaque, thereby addressing the pathology. Of the monoclonal antibodies being explored for AD, lecanemab has shown higher selectivity towards Aβ and better efficacy in clinical improvement. The phase III trials have demonstrated clinical improvement of mild AD upon biweekly intravenous administration of 10 mg/kg. This improvement was assessed using the primary and secondary endpoints such as Clinical Dementia Rating-Sum of Boxes (CDR-SOB), Mini-Mental State Examination (MMSE), and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). Apart from the infusion-related reactions with lecanemab, it is also associated with amyloid-related imaging abnormalities (ARIA), which are uniquely seen in monoclonal antibodies for AD as it is also seen in solanezumab and aducanumab. ARIA may be dose-dependent as with lower doses, the incidence was lower, and it is associated with microhemorrhages, hemosiderosis, or edema. Monoclonal antibodies such as aducanumab, agantenerumab have shown questionable efficacy; thus, their clinical use is debatable even though aducanumab has received FDA approval. Although solanezumab met some secondary endpoints, its benefit is similar to the placebo. Currently, efficacy is only proven for monotherapy with lecanemab; therefore, neurologists may need to discontinue adjuvant treatment. Clinical improvement in women and ApoE4 carriers is also questionable; further studies are required to prove its efficacy in these groups. Various studies are being conducted to find the efficacy of drugs targeting the complex pathology of AD, such as the tau targeting E2814, E2025 and E2511 protecting the cholinergic neurons, TREM2 agonists P522R prevent the microglial dysfunction. These drugs are noteworthy as they can be the possible combination of lecanemab. Further studies are required to prove lecanemab's efficacy in moderate-to-severe AD and its combination with other drugs.

Keywords Monoclonal antibodies, Lecanemab, Alzheimer's, Dementia, Neurodegeneration and beta-amyloid

Introduction

Alzheimer's disease (AD) is a devastating and progressive neurodegenerative disorder affecting millions worldwide. It significantly reduces the quality of life and increases dependency; cases have also shown that it can manifest as depression [1]. The nature of AD is multidisciplinary, and this can be understood by the various mechanisms behind its pathology. One of the most important mechanisms is the accumulation of beta-amyloid (Aβ) plaques in the brain [2], which further aggregate to form soluble oligomers, which leads to acute neuronal toxicity and neurodegeneration [3, 4]. Other mechanisms include tau hyperphosphorylation to form the neurofibrillary tangles, Calcium dysregulation, lysosome hypotheses [5],

*Correspondence:
Priti Dhande
pritidhande76@gmail.com
[1] Bharati Vidyapeeth (Deemed to Be University) Medical College, Pune-Satara Road, Dhankawadi, Pune, Maharashtra 411043, India

and mitochondrial dysfunction [6]. The neurodegenerative process implicated in AD affects various regions in the brain such as the entorhinal-hippocampal cortex, pons, locus ceruleus, tegmental areas, thalamus, hypothalamus, nucleus basalis of Meynert, habenula, putamen, caudate nucleus, ventricles, dura, cerebellum, amygdala, visual cortex, parietal cortex, temporal cortex, prefrontal cortex, cingulate cortex, and even optic nerve and spinal cord [7].

Various drugs are being formulated to target this complex neuropathology of AD and different brain regions to develop potential therapeutic interventions. Currently, aducanumab, gantenerumab, BAN2401, and ALZ-801 are some drugs that have gained attention through their anti-amyloid activity [8]. Lecanemab (BAN2401), an IgG1 monoclonal antibody, has shown a higher selectivity against soluble oligomeric and protofibrillar forms of Aβ [9]. In this review, we aim to provide a comprehensive evaluation of the current evidence on the pharmacokinetics, pharmacodynamics, mechanism of action, clinical trial results, side effects, potential in comparison to other therapies, and the future prospects of lecanemab which got the FDA approval in the treatment of AD.

Main text

Methodology

A systematic literature search was conducted using PubMed and Google Scholar databases for relevant articles. Keywords used in the search included "Lecanemab", "BAN2401", "Alzheimer's disease", "neurodegeneration", "Tau", "Dementia" and "Amyloid-beta". We included a balanced coverage of all the relevant and recent information available to show the development, potential, and limitations existing with the use of lecanemab in AD.

Pharmacokinetics and pharmacodynamics

Lecanemab is a monoclonal antibody administered via intravenous infusion [2]. Once administered, the drug binds to beta-amyloid protein in the brain and facilitates its clearance by the immune system.

McDade and colleagues, in their study showed that a dose of 10 mg/kg given biweekly significantly reduces brain amyloid (on PET scan), plasma tau and increases plasma Aβ42/40 highlighting a clinical improvement [10]. Maximum concentration and area under the plasma concentration–time curve values were dose-proportional over a 0.3–15 mg/kg dose range after a single dose [11]. Steady-state plasma concentration (SSPC) was achieved after 6 weeks with a dose of 10 mg/kg biweekly, and systemic accumulation was 1.4-fold. The terminal elimination half-life of lecanemab is 5–7 days, achieved by proteolytic enzymes similar to other IgG compounds [11].

The pharmacodynamics of lecanemab have been studied in various clinical trials. In a phase II study (NCT01767311), lecanemab 10 mg/kg IV every two weeks significantly reduced Aβ levels at 12 and 18 months relative to the placebo [12]. Such clinical improvement was found to be dose and time-dependent [13]. These improvements were correlated with reduced plasma tau 181 and increased plasma Aβ42/40, unlike placebo patients. Surprisingly, these positive trends reversed, and brain amyloid β plaque also increased during off-treatment, but after re-initiating the treatment, these trends were seen again [10]. Thus, lecanemab halts the disease progression and improves the patient's overall clinical profile of cognition, function, and daily activities.

Clinical trial results for lecanemab in patients with mild-to-moderate Alzheimer's disease

The efficacy and safety of lecanemab has been evaluated in various clinical trials. An 18-month, multicenter, double-blinded, placebo-controlled, phase 2 study with early AD included 854 patients (lecanemab 609; placebo 245) and demonstrated that lecanemab significantly reduced Aβ plaque burden [12]. Moreover, there was a significant improvement in clinical outcomes in patients regarding cognition, function, and activities of daily living.

The Phase III trial (Clarity AD/Study 301) was a randomized, double-blind, placebo-controlled study that included 1795 patients with mild cognitive impairment (MCI) due to AD or mild AD dementia. 897 received a placebo and 898 received lecanemab 10 mg/kg biweekly. This was a one of its kind study involving a diverse population with respect to race and comorbidities [14].

The primary endpoint was the change from baseline in the Clinical Dementia Rating-Sum of Boxes (CDR-SOB) score at 18 months, which was 1.21 in patients with lecanemab and 1.66 in placebo. The CDR-SOB is a widely used measure of dementia severity that assesses cognitive and functional abilities. This indicates a slower decline in cognitive function in patients treated with lecanemab [14].

Moreover, lecanemab showed significant improvement in secondary endpoints such as the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), and the Mini-Mental State Examination (MMSE) [15]. These results support the primary endpoint findings and demonstrate the potential clinical benefit of lecanemab in improving cognitive and functional outcomes in patients with AD.

Side effects and risks associated with lecanemab

When considering a treatment for any condition, assessing potential side effects and risks associated with the

medication is essential. Understanding the same allows for better prognostic assessment, patient compliance and management.

The most common adverse events associated with lecanemab were infusion-related reactions such as headaches, dizziness, and nausea. These adverse events were generally mild or moderate in severity and were more frequent in the higher-dose group [14, 15]. Death was noticed in 0.7% of participants on lecanemab and 0.8% in the placebo group.

Amyloid-related imaging abnormalities (ARIA) are commonly associated with cerebral micro hemorrhages, superficial siderosis, or edema of the brain parenchyma [15, 16]. Such ARIA is common with anti-Aβ antibodies, which may bind to cerebral amyloid angiopathy (CAA) or boost CAA production [17–19]. The incidence of ARIA was high in patients given higher drug dosage and in association with the presence of ApoE4 allele [20]. Patients who are ApoE4 carriers surprisingly showed enhancement in cognitive decline; this is concerning as genetic studies are rarely done in clinical practice before starting treatment [21]. Thus, AD patients who are ApoE4 carriers may show clinical worsening with lecanemab.

These adverse effects are unique to monoclonal antibodies compared to other drugs used for AD, such as cholinesterase inhibitors (donepezil, galantamine, and rivastigmine). Side effects such as ARIA with microhemorrhages or hemosiderosis or edema were also noted in patients who were given solanezumab in a phase 3 trial for preclinical AD [22] and even aducanumab [23].

Overall, the safety profile of lecanemab was favorable, and no new safety concerns were identified in the Phase III trial. The results suggest that lecanemab has a manageable safety profile, and the benefits of the treatment outweigh the risks.

Comparison with other AD treatments

Currently, very few treatment options are available for AD, which include cholinesterase inhibitors (such as donepezil, galantamine, and rivastigmine) which increase the levels of acetylcholine. The other option is the use of memantine, an NMDA receptor antagonist which regulates the activity of glutamate. These drugs only provide symptomatic relief without providing any disease-modifying action. Thus, the relief is temporary and reverses on stopping the medication as it provides no actual value as the primary pathology behind AD is not being addressed.

The current FDA-approved lecanemab, on the other hand, aids in disease reduction by acting on the key amyloid pathology in the brain, thereby slowing disease progression and delaying cognitive decline. Thus, not only does the patient achieve symptomatic relief, but the primary pathology is being targeted to achieve a complete resolve from the disease.

Efficacy of other monoclonal anti-amyloid Aβ antibody drugs

Aducanumab had two significant phase III clinical trials dubbed "ENGAGE" (NCT02477800) and "EMERGE" (NCT02484547) [24]. Both studies showed almost comparable results to the placebo [24]. Biogen subsequently terminated both studies due to interim post hoc analyses showing futility. What is more, the FDA still approved the drug in June 2021 [24]. Thus, its efficacy and practical use is highly questionable.

Gantenerumab also has shown some potential in AD. Doses up to 1200 mg, when administered subcutaneously once every four weeks, demonstrated a significant reduction in Aβ in patients with prodromal to moderate AD [25]. Further studies and phase III trials are required to prove its efficacy and subsequent FDA approval.

Solanezumab in phase 2 trials showed a reduction in beta-amyloid levels in the EXPEDITION 1 and 2 trial, although only in mild AD and no improvement in moderate AD. Even in mild AD patients, the results were almost comparable to placebo [26]. Even in EXPEDITION 3, a Phase 3 trial of solanezumab initiated in a mild AD patient population did not meet the primary objective of decreasing cognitive decline. Several secondary clinical endpoints, including cognitive and functional measures, did favor solanezumab, but the benefit was almost non-comparable [27].

Newer disease-modifying drugs in AD under research

As it stands, AD has a multifaceted pathology, and targeting these is of paramount importance. Currently, various trials are targeting tau proteins, microglial dysfunction, neurodegeneration, and many more pathologies involved in AD. Some of these are:

E2814 compound is being studied for its action against the tau protein's microtubule-binding region (MTBR), which is responsible for the trans-neuronal spread of neurofibrillary tangles [28, 29]. E2025 acts on the nerve growth factor pathway and prevents cholinergic cell loss [29]. E2511 promotes recovery and synaptic remodeling of damaged cholinergic neurons and suppresses cerebral atrophy caused by neurodegeneration [29].

Microglial dysfunction also plays an important role in the Alzheimer's disease process. Triggering receptor expressed on myeloid cells 2 (TREM2) agonists are being studied for microglial homeostatic maintenance and responses to AD-related inflammatory damage [30]. Drugs mimicking phospholipase C gamma 2 (PLCG2), a phospholipase-encoding gene expressed in microglia that has also been linked to the pathology of the disease.

Conversely, the variant of PLCG2, which is expressed by microglia, has shown protective effects against developing late-onset Alzheimer's in mouse studies [31].

These drugs are to be given special consideration as combination therapy with lecanemab or each other may be of much greater significance than monotherapy.

Practical considerations for using lecanemab

Lecanemab is a novel disease-modifying drug for AD. The drug has reached both its primary and secondary endpoints. Thus, it has established a good efficacy record in managing AD patients. Its clinical record is far superior to other monoclonal antibodies for AD currently under trial.

However, neurologists need to take several factors into account before prescribing it:

Currently, published results exist only for monotherapy trials with lecanemab in mild AD, and there is no evidence indicating safety or effectiveness when combined with other therapies or medications. As such, neurologists may need to reduce or discontinue other treatments before beginning lecanemab. The clinical efficacy of lecanemab still needs to be proven in patients with other comorbidities. Also, it has to be noted that clinical improvement of cognitive decline in women and ApoE4 carriers is still questionable [21].

These variables could lead to inconsistencies in its administration for the management of AD and potential errors that may jeopardize one's health and well-being.

Conclusion

In conclusion, the use of lecanemab for the treatment of AD represents a promising new approach while addressing the underlying disease process. Early clinical trial results suggest that the drug may be effective in reducing beta-amyloid levels in the brain and improving cognitive outcomes. While further research is needed to determine the optimal dosing, duration of treatment, and patient selection criteria, lecanemab has the potential to be a major advance in the treatment of AD. As of now intravenous infusion of lecanemab 10 mg/kg biweekly can be given to an AD patient with mild severity with no other comorbidities as a monotherapy to effectively improve the cognitive function and reduce the pathology.

Despite the challenges, the development of lecanemab and other similar drugs represents an important step forward in the fight against AD. As further research is conducted and more information becomes available, it will be important to carefully weigh the risks and benefits of lecanemab and other AD treatments by a neurologist to ensure that patients receive the most effective and holistic care possible.

Limitations and future directions

There are still several challenges to be overcome in the use of lecanemab. One major challenge is the cost of the drug, which is likely to be substantial and may limit its use in certain populations. Another challenge is the potential for side effects, particularly in the long-term use of the drug.

Further trials are required to prove lecanemab's efficacy in moderate-to-severe AD. The clinical implications of neuroprotective agents to prevent ARIA due to monoclonal antibodies in AD also need to be studied. Currently, results only exist for monotherapy with lecanemab, and subsequent studies showing the combined efficacy of lecanemab with drugs acting on different neuropathologies of AD may be of much more clinical significance. AD being a lifelong disorder, the long-term safety and efficacy can only be commented on when the drug meets actual clinical use.

Abbreviations

AD	Alzheimer's disease (devastating and progressive neurodegenerative disorder)
Aβ	Amyloid beta (Aβ accumulation in the brain is proposed to be an early toxic event in the pathogenesis of Alzheimer's disease)
SSPC	Steady-state plasma concentration
MCI	Mild cognitive impairment (early stage of memory loss or loss of language or visual/spatial perception)
CDR-SB	Clinical Dementia Rating-Sum of Boxes (global assessment tool which gives the global and Sum of Boxes (SOB) scores and the global score is used to stage dementia severity)
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale (testing tool used as a gold standard for assessing the efficacy of anti-dementia treatments)
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living (information about performance of Alzheimer's Disease patients in several activities of daily living are provided by their caregiver and its functional evaluation is done with this scale)
MMSE	Mini-Mental State Examination (30-point questionnaire used to measure cognitive impairment)
ARIA	Amyloid-related imaging abnormalities (abnormalities seen in magnetic resonance imaging of the brain in patients with Alzheimer's disease)
CAA	Cerebral amyloid angiopathy
TREM	Triggering receptor expressed on myeloid cells 2
PLCG2	Phospholipase C gamma 2
MTBR	Microtubule-binding region

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Author contributions

AT analyzed the available studies and was a major contributor for writing the manuscript. PD gave the practical considerations part of using the drug and cross checked each and every part of the manuscript. Both the authors read and approved the final manuscript.

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