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Review Article On Lequembi (Lecanemab): Advancing Alzheimer`S Therapy Through Monoclonal Antibody Innovation

[1*]Ms.Vaishnavi K. Chivte, [2]Mr.Mayur Pramod Gadakh, [3]Dr.Vijaykumar Kale,[4]Dr.Mahesh Thakare,[5]Mr.Vaibhav Narwade,[6]Ms.Dhanashree K. Chivte

[1]Assistant professor, [2]Student, [3]Principal,[4]Assistant professor,[5]Assistant professor,[6]Assistant professor

[1]Pharmaceutical chemistry,

[1]Kasturi Shikshan Sanstha college of pharmacy,Shikrapur,Pune,India.

*-corresponding author- Ms.Vaishnavi K. Chivte

ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia and remains one of the greatest challenges in modern medicine. Current treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, only provide symptomatic relief without slowing disease progression. In recent years, monoclonal antibodies targeting amyloid-beta (Aβ) pathology have gained attention as potential disease-modifying therapies. Among these, Leqembi (lecanemab) has emerged as a milestone in Alzheimer's research and treatment.

Leqembi is a humanized IgG1 monoclonal antibody that binds selectively to soluble amyloid-beta protofibrils, preventing their aggregation into insoluble plaques and enhancing their clearance by immune mechanisms. By targeting the root pathological process, it helps reduce amyloid burden and slows neurodegeneration. The Phase III CLARITY-AD clinical trial (2022) demonstrated that lecanemab slowed cognitive and functional decline by approximately 27% in early-stage Alzheimer's patients compared with placebo.

Despite its promise, challenges remain. The most notable adverse effects are amyloid-related imaging abnormalities (ARIA), including brain edema and micro-hemorrhages, which require careful MRI monitoring. High cost, limited accessibility, and the need for further long-term studies also restrict its widespread use.

In conclusion, the approval of Leqembi in 2023 by the FDA represents a significant shift from symptomatic management to disease-modifying therapy in Alzheimer's disease. This project reviews its pharmacology, clinical benefits, safety concerns, and future prospects, highlighting its role as a groundbreaking step in neurodegenerative drug development.

KEYWORDS: Leqembi, Lecanemab, Alzheimer's disease, Monoclonal antibody, Amyloid-beta, Neurodegeneration.

INTRODUCTION

Alzheimer's disease (AD) is recognized as the leading cause of dementia globally and poses a significant healthcare challenge in the 21st century. This chronic and irreversible neurodegenerative disorder is characterized by memory loss, cognitive deterioration, behavioral changes, and a decline in functional independence.

According to the World Health Organization (WHO), over 55 million people worldwide live with dementia, with AD constituting about 60–70% of these cases. As lifespans increase and populations age, the incidence of AD is projected to rise considerably, highlighting the urgent need for effective treatments.

Historically, the management of Alzheimer's disease has primarily focused on symptom relief. Medications like donepezil, rivastigmine, and galantamine (which function as cholinesterase inhibitors), along with memantine (an NMDA receptor antagonist), are commonly used to improve cognitive performance and slow symptom progression. However, these treatments fail to address the disease's underlying mechanisms, with their impacts often being short-lived and limited. Consequently, the development of disease-modifying therapies (DMTs) has become a key area of research in recent years.

The biology of AD is complex and involves multiple processes, with one of its main characteristics being the accumulation of amyloid-beta (Aβ) peptides in the brain. These peptides form both soluble protofibrils and insoluble plaques, which interfere with neuronal communication, trigger inflammation, and lead to ongoing neurodegeneration. Besides amyloid accumulation, the pathological clumping of tau protein into neurofibrillary tangles also contributes to the disease's progression. Nonetheless, targeting amyloid-beta has become the most actively pursued therapeutic strategy lately, resulting in the development of monoclonal antibodies aimed at clearing amyloid deposits.

Leqembi (lecanemab), a humanized monoclonal antibody, has emerged as a particularly promising candidate in this domain. Unlike earlier anti-amyloid therapies that failed to show significant clinical benefits, lecanemab specifically targets soluble Aβ protofibrils, which are recognized as highly harmful precursors to plaque formation. By facilitating their removal and preventing further aggregation, lecanemab decreases the amyloid burden in the brain and slows neurodegeneration.

The approval of Leqembi by the FDA in January 2023 marks a significant breakthrough in Alzheimer's research. It represents the first treatment to demonstrate a statistically significant reduction in both cognitive and functional decline in patients in the early stages of Alzheimer's disease. Findings from the Phase III CLARITY-AD trial revealed a 27% reduction in disease progression compared to a placebo, instilling hope that disease modification may become a viable option for AD.

Despite these advancements, numerous challenges remain. Leqembi is linked to amyloid-related imaging abnormalities (ARIA), including cerebral edema and micro-haemorrhages, necessitating vigilant MRI monitoring. Additionally, the treatment's high cost, requirement for intravenous administration, and limited availability present obstacles to its broad adoption at this stage. Nevertheless, its approval has rekindled optimism for millions affected by Alzheimer's disease and has opened avenues for further exploration of combination therapies, earlier interventions, and personalized treatment strategies.

This project paper aims to provide a comprehensive review of Leqembi (lecanemab), outlining its pharmacological mechanisms, clinical trial outcomes, safety profile, advantages, challenges, and future possibilities. By assessing both its strengths and drawbacks, this work seeks to underscore the significance of lecanemab in transforming the treatment landscape for Alzheimer's disease and advancing the development of disease-modifying therapies in the field of neurodegeneration.

Ç Significance of the Study

Alzheimer's disease not only affects patients but also places a tremendous emotional, social, and economic burden on families and healthcare systems worldwide. Traditional therapies provide only temporary relief, highlighting the urgent need for treatments that can alter disease progression.

Leqembi (lecanemab) is a landmark in this regard — representing a paradigm shift from managing symptoms to directly addressing the underlying cause of Alzheimer's disease. Its successful development and FDA approval demonstrate the potential of monoclonal antibodies to change the course of neurodegenerative disorders.

This study is therefore significant as it:

Highlights the evolution of targeted immunotherapy in neurodegeneration. Reviews key scientific and clinical milestones in the development of lecanemab. Emphasizes the need for early diagnosis and intervention in Alzheimer's disease.
Serves as a foundation for future research combining traditional neurology with modern biotechnology.

By studying Leqembi's journey, this project aims to enhance understanding of advanced biologic drug development and inspire continued innovation in the search for effective Alzheimer's treatments.

1990s – Amyloid Hypothesis Proposed

↓

2001 – Discovery of Soluble Amyloid-beta Protofibrils (Toxic Form)

↓

2007 – Development of BAN2401 (Preclinical Monoclonal Antibody Candidate)

↓

2012 – Start of Phase I Clinical Trials (Safety & Tolerability)

↓

2018 – Phase IIb Study Demonstrates Reduction in Amyloid Burden

↓

2020 – Initiation of CLARITY-AD Phase III Trial

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2022 – Phase III Results Show 27% Slowing of Cognitive Decline

↓

Jan 2023 – FDA Grants Accelerated Approval

↓

July 2023 – Full Traditional FDA Approval for Early Alzheimer's Disease

Fig No.1: Timeline of Leqembi (Lecanemab) Development and Approval [8]

MECHANISM OF ACTION [19,20]

Leqembi (lecanemab) is a humanized IgG1 monoclonal antibody specifically designed to target amyloid-beta (Aβ) protofibrils [19], which are considered one of the most toxic forms of amyloid aggregates in Alzheimer's disease. Unlike older therapies that only targeted insoluble amyloid plaques, lecanemab focuses on the soluble, intermediate structures that directly contribute to neurotoxicity and cognitive decline.

The mechanism of action can be understood in the following steps:

1. Binding to Amyloid-Beta Protofibrils

Lecanemab selectively binds to soluble amyloid-beta protofibrils with high affinity.

Protofibrils are toxic intermediates formed during the aggregation of Aβ peptides into insoluble fibrils and plaques.

By binding to these protofibrils, lecanemab prevents their further aggregation into plaques.

2. Clearance of Amyloid-Beta Aggregates [20]

Once bound, lecanemab tags the protofibrils for clearance by the immune system.

Microglial cells, the brain's resident immune cells, recognize the antibody-protofibril complex and phagocytose (engulf) it.

This leads to a reduction in amyloid burden in the brain.

3. Prevention of New Plaque Formation

By targeting early soluble forms, lecanemab prevents the seeding process that leads to new amyloid plaque formation.

This halts further deposition of insoluble Aβ in neuronal tissues.

4. Neuroprotection

Reduction in amyloid burden decreases neuronal toxicity, inflammation, and synaptic dysfunction.
This translates into slower cognitive and functional decline in patients with Alzheimer's disease.

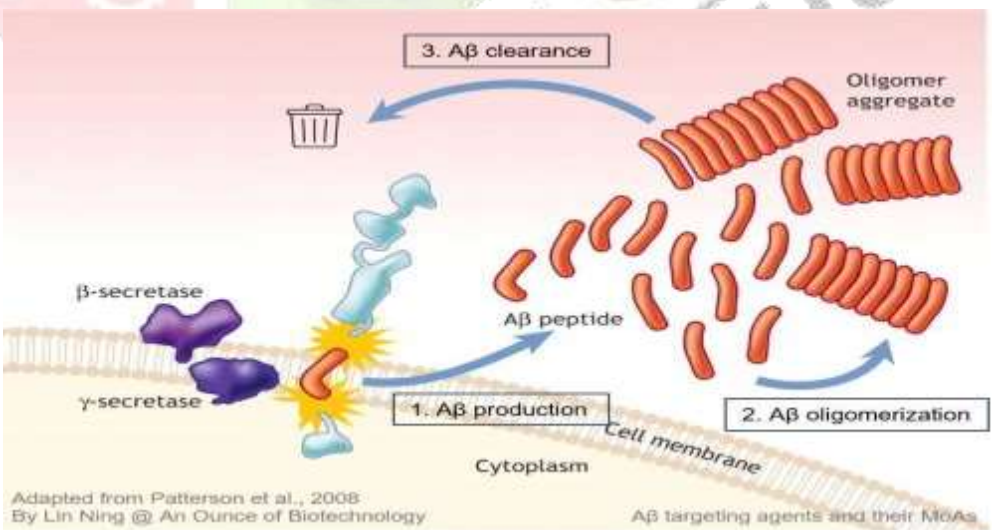

Fig No.2: Mechanism of action of leqembi (Lecanemab) in Alzheimer`s Disease [21]

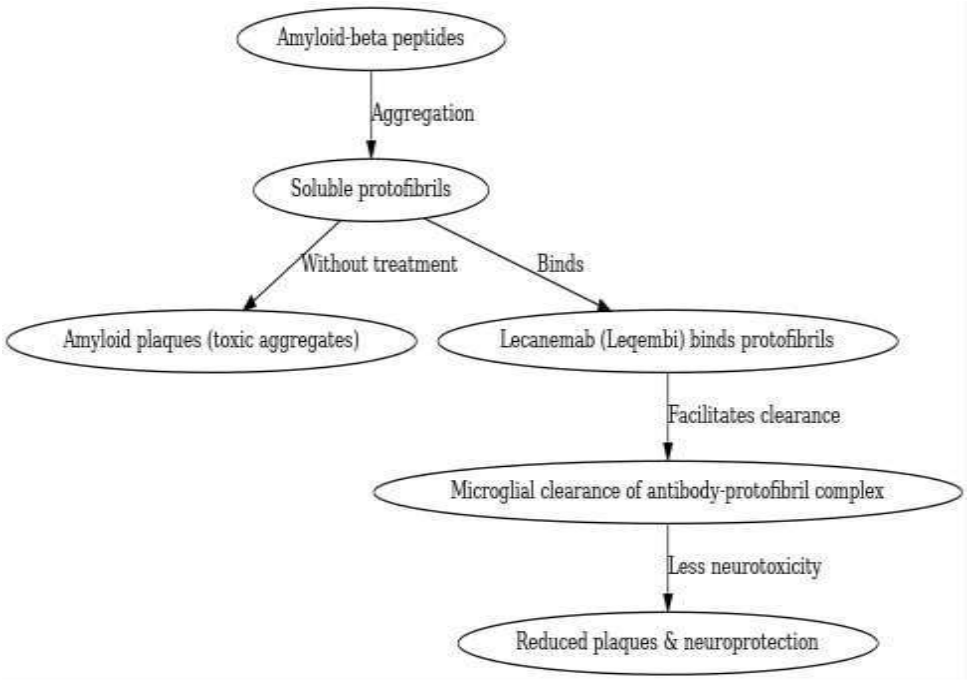

Fig No.3: Mechanism of action of leqembi (Lecanemab) in Alzheimer`s Disease[21]

CLINICAL EFFICACY

The effectiveness of Leqembi (lecanemab) has been thoroughly researched in various clinical trials, from early Phase II investigations to the extensive Phase III CLARITY-AD trial. These studies demonstrate that lecanemab not only decreases amyloid-beta load in the brain but also slows down cognitive and functional decline in
individuals with Alzheimer's disease.

1. Phase IIb Study (Swanson et al., 2021) [13]

This trial was a multicenter, randomized, placebo-controlled study that involved 856 patients diagnosed with early-stage Alzheimer's disease. Treatment with lecanemab resulted in a dose-dependent decrease in amyloid- beta levels, as evidenced by PET imaging. Patients who received the highest dosage (10 mg/kg biweekly)
exhibited a notable reduction in plaque compared to the placebo group. Notably, beginning treatment early and continuously was associated with greater clinical improvements, reinforcing the notion of early intervention in Alzheimer's disease.

2. CLARITY-AD Phase III Trial (Van Dyck et al., 2023) [9]

This trial included 1,795 patients exhibiting mild cognitive impairment or mild Alzheimer's disease dementia with confirmed amyloid pathology. Participants were randomly assigned to receive either lecanemab (10 mg/kg IV every two weeks) or a placebo for an 18-month period.

The outcome revealed a 27% reduction in the rate of cognitive and functional decline on the Clinical Dementia Rating–Sum of Boxes (CDR-SB) scale. There was significant improvement in daily functional abilities in comparison to the placebo group. Sustained reductions in amyloid plaque levels were confirmed through PET scans. These results positioned lecanemab as one of the first therapies capable of modifying the course of Alzheimer's disease.

3. Long-Term Extension Studies [17]

Follow-up studies indicate that ongoing treatment with lecanemab continues to achieve amyloid clearance and may lead to incremental clinical benefits over extended durations. Current trials are exploring whether initiating treatment before the onset of severe symptoms could result in even better outcomes.

4. Comparative Outcomes

In comparison to aducanumab, lecanemab exhibited:
Greater selectivity for soluble protofibrils, More consistent clinical advantages,
A lower rate of severe side effects.

Donanemab, another anti-amyloid antibody, has also shown potential, but lecanemab is the first to receive traditional FDA approval based on strong Phase III evidence.

Lecanemab has consistently proven its ability to diminish amyloid plaque load and impede disease progression in patients with early-stage Alzheimer's disease. The CLARITY-AD trial marks a significant milestone by confirming that disease modification is achievable through targeted amyloid-beta interventions. While further long-term safety assessments and real-world data are required, lecanemab has ushered in a new phase in the treatment of Alzheimer's.

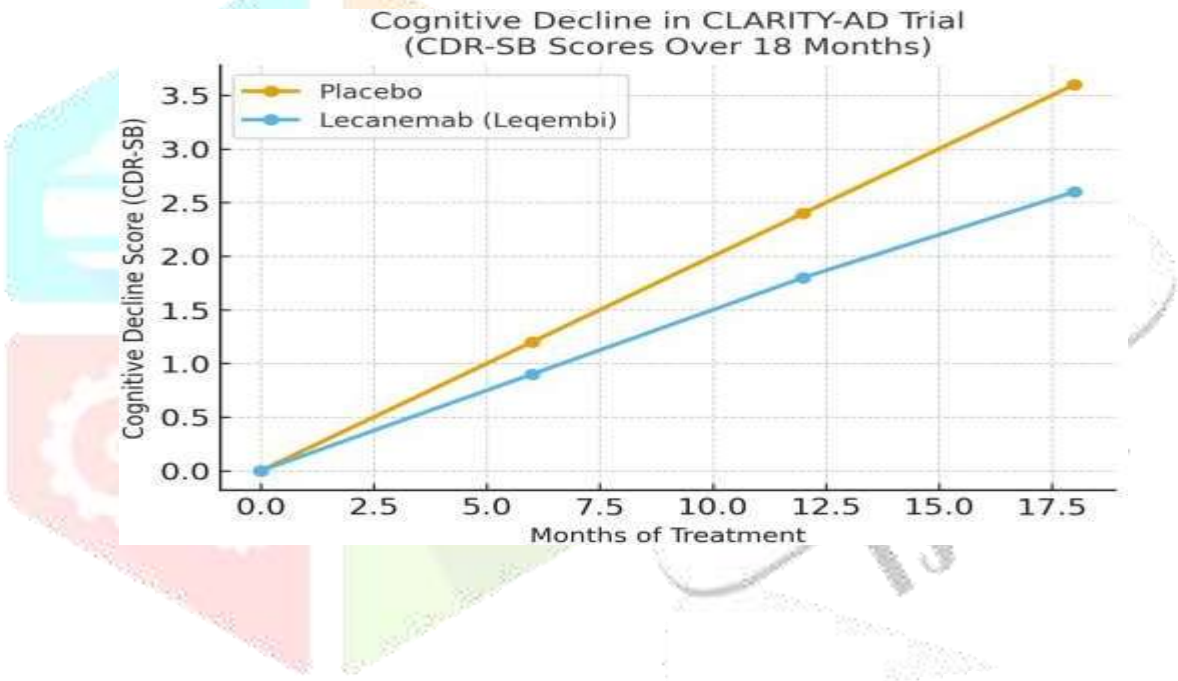

Fig No.4: Cognitive Decline in CLARITY-AD Trial (CDR-SB Scores Over 18 Months) [9]

SAFETY AND ADVERSE EFFECT

While Leqembi (lecanemab) has shown significant clinical efficacy in slowing the progression of Alzheimer's disease, its use is associated with certain risks and adverse effects that must be carefully monitored. The most notable safety concern is the occurrence of amyloid-related imaging abnormalities (ARIA), which have been observed with most monoclonal antibodies targeting amyloid-beta.

1. Amyloid-Related Imaging Abnormalities (ARIA) ARIA-H (Hemorrhage) [14]:
Small areas of bleeding or microhemorrhages in the brain. This can occasionally lead to seizures or stroke-like symptoms. In the CLARITY-AD Phase III trial, ARIA was reported in ~21% of lecanemab-treated patients, compared to 9% in the placebo group.

Most cases were mild to moderate and resolved either spontaneously or with treatment interruption.
ARIA-E (Edema or effusion) [20]:

Swelling in the brain tissue detected on MRI scans. Symptoms may include headache, confusion, dizziness, nausea, or vision disturbances.

2. Infusion-Related Reactions

Since lecanemab is administered intravenously, some patients experienced infusion-related side effects, including: Fever, chills, rash, nausea, or changes in blood pressure.

These reactions are typically mild and can be managed with supportive care.

3. Headache and Fatigue

A subset of patients reported headaches, fatigue, and general malaise following infusions. These symptoms were usually temporary and non-serious.

4. Risk Factors for Adverse Effects

Patients carrying the APOE ε4 gene variant are at higher risk of developing ARIA.
Therefore, genetic testing and close MRI monitoring are recommended before and during therapy.

5. Monitoring and Management [21]

Patients receiving lecanemab require regular brain MRI scans to detect ARIA early.
If moderate to severe ARIA is detected, treatment may need to be paused or discontinued. Supportive therapy and gradual reintroduction may be considered in some cases.
Leqembi is generally well tolerated, but ARIA remains the most significant safety concern, requiring careful monitoring. Infusion-related reactions and mild headaches are other common side effects. Despite these risks, the benefits of slowing cognitive decline in early Alzheimer's disease make lecanemab a valuable therapeutic option when administered with proper safety precautions.

Aspect of Key Findings	
Efficacy	27% slowing of cognitive decline (CLARITY-AD Trial)
Amyloid Clearance	Significant reduction amyloid plaques on PET imaging
Safety Area	Observed in ~21% of treated patients
Tolerability	Mostly mild to moderate reactions
Clinical Use	Best Suited for early-stage Alzheimer`s patients under RImonitoring

Table1: Summary of Clinical and Safety Findings

The clinical and safety outcomes of Leqembi (lecanemab) together establish a significant therapeutic milestone in Alzheimer's management. The drug has shown a 27% reduction in disease progression, confirming that direct targeting of soluble amyloid-beta protofibrils can truly modify the course of neurodegeneration rather than merely controlling symptoms. PET imaging evidence has demonstrated consistent amyloid clearance across patient populations, supporting the amyloid hypothesis that has guided decades of research.

Although the therapy is associated with amyloid-related imaging abnormalities (ARIA), including edema and microhemorrhages, these effects are largely manageable with careful MRI monitoring and dose adjustments. Infusion-related reactions such as headache or fatigue are generally transient and mild.

APPLICATIONS AND ADVANTAGES

Leqembi (lecanemab) represents one of the most significant therapeutic advances in Alzheimer's disease management in recent decades. Its approval provides not only a new treatment option but also a new hope for patients, families, and healthcare providers. The applications and advantages of lecanemab can be described as follows:

1. Disease Modification Rather than Symptom Control [11]

Traditional drugs for Alzheimer's disease (donepezil, rivastigmine, galantamine, memantine) only manage symptoms temporarily.

Leqembi is the first therapy proven to slow disease progression by targeting amyloid-beta pathology. This makes it a disease-modifying therapy (DMT) instead of a symptomatic treatment.

2. Early Intervention in Alzheimer's Disease

The drug is approved for use in patients with mild cognitive impairment (MCI) or mild Alzheimer's dementia.
This allows treatment before irreversible brain damage occurs, leading to better preservation of memory and function.

3. Improvement in Cognitive and Functional Outcomes

Clinical trial results demonstrated a 27% slowing of decline in cognition and daily activities.
Patients maintained better ability to perform everyday tasks, improving quality of life and independence.

4. Reduction of Amyloid Plaque Burden [13]

PET imaging studies confirmed that lecanemab significantly reduces amyloid plaque levels in the brain.
This provides strong biological evidence of its effectiveness and supports the amyloid hypothesis of Alzheimer's.

5. Foundation for Future Combination Therapies

By successfully validating amyloid clearance, lecanemab opens the door for combination treatments (amyloid + tau therapies).

Future regimens may become more effective by addressing multiple pathological targets.

Global Impact on Alzheimer's Research

Leqembi's approval by the FDA has reignited scientific and pharmaceutical interest in Alzheimer's research.
It represents a model for the development of other monoclonal antibody-based treatments in neurodegeneration.
Leqembi is not just another Alzheimer's drug — it is the first to prove disease-modifying potential. Its advantages include slowing cognitive decline, reducing amyloid plaque burden, enabling earlier treatment, and paving the way for future therapies. While challenges remain regarding cost and monitoring, its approval marks a historic milestone in the fight against dementia

Mechanism and Therapeutic Impact of Leqembi

Leqembi (Lecanemab) works by selectively binding to soluble amyloid-beta protofibrils, which are the toxic forms responsible for neuronal damage and cognitive decline in Alzheimer's disease. The following schematic flow explains its overall mechanism and therapeutic pathway:

Amyloid-beta formation
↓
Soluble protofibrils (toxic intermediates)
↓
Leqembi binding to protofibrils
↓
Immune activation (microglial clearance)
↓
Reduction of amyloid plaque burden
↓
Improved neuronal function
↓
Slower cognitive and functional decline

Fig no 5: Overall pathway showing the mechanism of action and clinical benefits of Leqembi (Lecanemab).

This graphical abstract summarizes the entire therapeutic process of Leqembi — from amyloid-beta formation to clinical benefit. By focusing on the earliest and most toxic stage of amyloid aggregation, it prevents plaque formation, reduces inflammation, and helps maintain neuronal integrity. The mechanism not only demonstrates the precision of modern monoclonal antibody therapy but also highlights the transition of Alzheimer's treatment from symptomatic control to true disease modification.

FUTURE PROSPECTS

The authorization of Leqembi (lecanemab) has marked a significant milestone in the field of Alzheimer's disease treatment. It is the first drug to exhibit a clinically meaningful reduction in disease progression by addressing the root amyloid-beta pathology, rather than just alleviating symptoms. However, its achievements also lay the groundwork for the creation of more sophisticated and patient-friendly therapeutic options in the future. The following elements highlight the most encouraging future avenues for research and clinical utilization of Leqembi and similar monoclonal antibodies.

1. Early Diagnosis and Integration of Artificial Intelligence [11]

Timely identification of Alzheimer's disease is crucial for effective intervention, as Leqembi is most effective during the early stages of cognitive decline. The application of artificial intelligence (AI), machine learning, and digital biomarkers can assist in identifying subtle cognitive changes even years before the onset of clinical symptoms. AI-enhanced imaging analysis and smart wearable devices may soon facilitate remote monitoring of brain health, leading to prompt therapeutic measures.

2. Strategies for Combination Therapy [12]

Given that Alzheimer's disease encompasses various pathogenic pathways, future treatment is likely to depend on combination therapies instead of isolated drug solutions. Researchers are investigating the potential of pairing Leqembi with anti-tau antibodies, anti-inflammatory medications, neuroprotective peptides, or antioxidant formulations. Such combinations could simultaneously address both amyloid and tau pathologies, offering stronger and more sustained control of the disease.

3. Approaches in Personalized and Precision Medicine [12]

The future of Alzheimer's care will more frequently emphasize tailored treatments based on patient history, genetic analysis, and individual risk factors. Biomarkers such as amyloid PET imaging, plasma Aβ42/40 ratios, tau phosphorylation levels, and neurofilament light chain (NfL) could assist in identifying which patients are most likely to gain from Leqembi treatment. Customized dosing and monitoring will aid in reducing side effects while enhancing effectiveness.

4. Progress in Developing Subcutaneous and Oral Formulations [15]

At present, Leqembi is delivered via intravenous (IV) infusion biweekly. Researchers are now working on creating subcutaneous formulations that patients can administer themselves at home. This method would simplify treatment, lessen hospital reliance, and enhance patient adherence. In the future, there is also optimism for the development of oral antibody mimetics or nanoparticle-based oral delivery systems, potentially transforming Alzheimer's treatment by increasing convenience and adherence.

5. Advancements in Antibody Engineering [18]

Ongoing progress in biotechnology and protein engineering is anticipated to yield next-generation monoclonal antibodies with enhanced selectivity, better penetration of the blood-brain barrier, and extended half-lives. Altered antibody fragments or bispecific antibodies might offer stronger attraction to amyloid protofibrils with fewer side effects. Such advancements could also lead to reduced production costs, making biologic medications more accessible worldwide.

6. Incorporation of Ayurveda and Herbal Nanomedicine [23]

Future investigations may also explore the combination of traditional medicine principles with advanced delivery systems. Herbal ingredients known for their neuroprotective properties—such as curcumin, ashwagandha, and bacopa—could be integrated into nanocarriers along with monoclonal antibody treatments. These Ayurveda- based nanomedicine strategies may provide combined benefits by merging natural antioxidants with biologics that modify disease progression.

The outlook for Alzheimer's treatment is optimistic, with Leqembi representing the initial move toward curative and preventative therapies. The next decade is projected to see the emergence of more effective, affordable, and safer alternatives to monoclonal antibodies. With ongoing developments in biotechnology, artificial intelligence, and nanomedicine, it is conceivable that Alzheimer's disease could one day be a fully manageable or even preventable condition**.**

7. The integration of nanotechnology with biologic therapies

holds great promise. Nanocarriers such as liposomes, polymeric nanoparticles, and dendrimers can successfully transport antibodies like Leqembi directly into the brain, improving targeting while reducing systemic side effects. These nanomedicine delivery mechanisms have the potential to revolutionize how Alzheimer's medications are delivered across the blood–brain barrier.

8. Global Collaboration and Policy Development

The future success of Alzheimer's treatments will depend not only on scientific advancements but also on global health policies. Collaboration between governments, pharmaceutical companies, and international organizations is crucial to improve access to biologic therapies. Large-scale collaborations can help reduce costs, promote technology transfer, and implement screening programs for early detection. Increasing public awareness and offering training for caregivers will also play a significant role in the overall success of treatment.

Leqembi has not only changed the current treatment landscape but has also initiated a wave of innovation that will propel future progress in the study of neurodegenerative disorders. Its success exemplifies how targeted molecular therapies, patient-centered care, and committed scientific endeavors can together enhance human health outcomes.

LIMITATIONS AND CHALLENGES

Although Leqembi (lecanemab) represents a revolutionary advance in Alzheimer's therapy, several limitations and challenges continue to restrict its broad clinical use. These limitations arise from safety concerns, cost-related issues, and the complexity of treatment procedures.

1. Restricted Use to Early-Stage Alzheimer's Disease [1]

Clinical benefits of lecanemab are mainly evident in mild cognitive impairment or early Alzheimer's disease. In moderate or advanced stages, therapeutic effects remain unclear.

2. Intravenous Route of Administration

The requirement of biweekly intravenous infusions under medical supervision adds inconvenience and dependence on healthcare facilities. This limits its use in rural or low-resource settings.

3. Amyloid-Related Imaging Abnormalities (ARIA)

ARIA remains the most significant adverse event associated with lecanemab. It includes cerebral edema and microhemorrhages, which demand frequent MRI scans and close neurological monitoring.

4. High Cost and Limited Accessibility [25]

Leqembi is extremely expensive, making it unaffordable for most patients. Developing nations face major financial barriers in obtaining biologic drugs like monoclonal antibodies.

5. Lack of Long-Term Data

While short-term studies confirm reduced amyloid burden and slower decline, long-term benefits on survival and sustained cognition are not yet established.

6. Ethical and Social Considerations [25]

The need for genetic testing (especially APOE ε4 carriers) and the high treatment cost raise ethical and social challenges in equitable patient selection.

In summary, Leqembi's introduction marks a major scientific success but also highlights the difficulties of translating cutting-edge biotechnology into universally accessible treatment. Future improvements in delivery methods, cost-effectiveness, and patient monitoring will be essential to overcome these challenges and fully realize its therapeutic potential.

CONCLUSION

Leqembi (lecanemab) represents one of the most significant scientific milestones in the modern history of Alzheimer's disease research. For decades, researchers struggled to develop a therapy that could truly modify the course of this devastating neurodegenerative disorder rather than merely alleviate symptoms. Leqembi has achieved that goal by specifically targeting soluble amyloid-beta protofibrils, which are now recognized as the most neurotoxic species responsible for synaptic damage, neuronal death, and progressive memory loss. Its mechanism has validated the long-debated amyloid hypothesis and provided clinical proof that early and precise intervention can indeed alter disease progression. Leqembi's journey from laboratory discovery to regulatory approval is not just a scientific success story but a testament to decades of perseverance, collaboration, and innovation. It has inspired a new era of precision medicine in neurology — one that prioritizes early diagnosis, molecular targeting, and patient-centered care. In conclusion, Leqembi symbolizes a new dawn in Alzheimer's therapy. It has transformed despair into

determination and uncertainty into scientific confidence. While challenges remain, the foundations it has laid will guide the future of neurotherapeutic development. With ongoing research, technological progress, and global collaboration, Leqembi stands as a beacon of hope that the battle against Alzheimer's disease can one day be won.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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