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Advancements in Early Alzheimer's Treatment: Narrative Review about Lecanemab (Leqembi ®)

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Abstract:

Alzheimer's disease represents one of the most significant challenges in the field of neurology, affecting millions of individuals worldwide. In pursuing efficacious treatments, lecanemab has emerged as a promising therapeutic option. This pioneering monoclonal antibody targets and reduces amyloid-beta plaques in the brain, a defining feature of Alzheimer's disease. By addressing one of the fundamental causes of the disease, lecanemab represents a novel approach to slowing its progression.

On 14th November 2024, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending granting marketing authorisation for Leqembi® (whose active substance is lecanemab). This recommendation is specifically directed towards patients with early-onset Alzheimer's disease who are non-carriers or heterozygotes for the apolipoprotein E ε4 (ApoE ε4) allele, thereby underscoring the drug's efficacy tailored to specific genetic profiles (Committee for Medicinal Products for Human Use, 2024).

The CHMP's approval is a testament to the extensive research and clinical trials that have demonstrated the efficacy and safety of Leqembi® (Lecanemab). This narrative review aims to provide a comprehensive examination of these aspects and offer a detailed understanding of the potential impact of this treatment on the management of early Alzheimer's disease.

Keywords: Leqembi, Lecanemab, Alzheimer’s disease, BAN2401

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder. As the most common cause of dementia worldwide, AD is an increasingly important public health problem, with a predicted threefold increase in incidence over the next 50 years (Vitek et al., 2023; Abdelazim et al., 2024). The pathophysiology of Alzheimer's disease is linked to the Amyloid Cascade Hypothesis (ACH), which proposes that the accumulation of Aβ is the primary trigger for a series of molecular events that ultimately lead to the production of hyperphosphorylated tau aggregates, the activation of neuronal death mechanisms, and ultimately dementia (Granzotto & Sensi, 2024). The above triad is known as the Alzheimer's disease continuum and forms the basis of the "ATN Research Framework", where "A" stands for amyloid, "T" for tau

and "N" for neurodegeneration. (Granzotto and Sensi, 2024) One of the challenges associated with the management of this disease is the need for symptomatic treatment, as there is currently a lack of disease-modifying pharmacotherapy.

On 14th November 2024, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending granting a marketing authorisation for Leqembi®. This recommendation was made specifically for patients with early-onset Alzheimer's disease who are non-carriers or heterozygotes for the apolipoprotein E ε4 (ApoE ε4) allele. This targeted approval reflects a strategic shift towards personalised medicine, ensuring that those most likely to benefit from the treatment receive it.

The CHMP's decision follows an exhaustive re-examination process that included a comprehensive evaluation of clinical trial data, safety profiles and the drug's mechanism of action. This thorough review ensures that Leqembi® meets the high efficacy and safety standards before reaching patients. The CHMP's positive recommendation not only facilitates the availability of Leqembi® on the European market but also sets a precedent for future Alzheimer's treatments using a targeted, genetically informed approach.

The active ingredient in Leqembi® is **lecanemab**, also known as BAN2401. Its efficacy has been demonstrated due to its distinctive mechanism of action, which explicitly targets the amyloid-beta peptides responsible for forming plaques in the brain (Chowdhury & Chowdhury, 2023). By targeting the toxic protofibrils of amyloid-β, lecanemab may have a disease-modifying effect that slows the progression of cognitive and functional deficits in AD patients, which can help improve the quality of life for patients with mild AD and their families. (Abdelazim et al. 2023)

A detailed search was conducted using PubMed, Cochrane, and ClinicalTrials.gov to guarantee a comprehensive and up-to-date literature synthesis. The search terms "lecanemab", "Leqembi", and "BAN2401" were used to identify over 30 peer-reviewed articles, including clinical trials, meta-analyses, and systematic reviews, published in the past five years. Relevant literature sources were restricted to 23 papers written in English during the study. Only completed trials were chosen to extract data concerning the therapeutic outcomes, safety profiles and comparative efficacy of lecanemab.

Mechanism of Action

Lecanemab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively targets soluble aggregated Aβ species (protofibrils) with activity at amyloid plaques.

(Vitek et al., 2023) Targeting these peptides facilitates their clearance from the brain, thereby reducing the burden of amyloid plaques and potentially slowing cognitive decline. Johannesson et al. (2024) state that lecanemab can bind to Aβ plaques while demonstrating a preference for targeting soluble aggregated Aβ protofibrils and established plaques. Furthermore, lecanemab has a diminished binding affinity for Aβ40-enriched fibrils, limiting its interaction with cerebral amyloid angiopathy (CAA). The hypothesis posits that CAA may trigger a cascade of events leading to fluid and potentially blood leakage into the brain parenchyma, a process that may culminate in ARIA. These findings indicate that this antibody is well-positioned to facilitate plaque clearance in patients with Alzheimer's disease while reducing the likelihood of adverse effects. Moreover, it has been demonstrated that soluble Aβ aggregates are more neurotoxic than monomers and insoluble fibrils. (Söderberg et al., 2023) Consequently, it can be postulated that removing these soluble Aβ aggregates would constitute an efficacious approach for treating AD.

The drug's capacity to selectively target amyloid-beta represents a notable advancement in the field. Conventional therapeutic modalities frequently concentrate on providing symptomatic relief, whereas lecanemab targets the underlying pathophysiology of Alzheimer's disease. This targeted approach offers therapeutic benefits and a foundation for further research into disease-modifying treatments.

Clinical Trials and Efficacy

Several pivotal clinical trials have been conducted to assess the efficacy of lecanemab. These multinational, multicentre studies, published in esteemed journals such as Alzheimer's Research & Therapy and The New England Journal of Medicine, collectively involved thousands of participants across various regions and have provided substantial evidence supporting the drug's use in slowing cognitive decline in patients with early-stage Alzheimer's.

Lecanemab was assessed in the **Study 201** Core, an 18-month, phase 2 proof-of-concept, double-blind study (NCT01767311) utilising a Bayesian design with response-adaptive randomisation in 856 patients diagnosed with early-stage Alzheimer's disease (mild cognitive impairment due to AD or mild AD dementia) (Swanson et al., 2021). Furthermore, the study included an open-label extension phase, allowing patients to receive open-label lecanemab 10 mg/kg biweekly for up to 24 months. (McDade et al., 2022) The primary endpoint was clinical change at 12 months on the Alzheimer's Disease Composite Score (ADCOMS). Secondary endpoints included a reduction in brain Aβ loads as observed on positron emission

tomography (PET), clinical decline as measured on the Alzheimer's Disease Composite Score (ADCOMS), Clinical Dementia Rating-Sum of Boxes (CDR-SB), the AD Assessment Scale-Cognitive Subscale (ADAS-Cog), changes in cerebrospinal fluid (CSF) core biomarkers (Aβ40, Aβ42, total tau, phospho-tau), and changes in total hippocampal volume as determined by volumetric magnetic resonance imaging. (Swanson et al. 2021)

The 10 mg/kg biweekly dosage of lecanemab demonstrated a 64% probability of exhibiting superior efficacy to placebo by 25% on ADCOMS at 12 months. However, this did not reach the 80% threshold set as the primary endpoint. At 18 months, the dosage mentioned above demonstrated a 27% and 30% reduction in decline on the ADCOMS, a 56% and 47% reduction on the ADAS-Cog, and a 33% and 26% reduction on the CDR-SB, as compared to placebo, according to Bayesian and frequentist analyses, respectively. Furthermore, this dosage of lecanemab resulted in a notable reduction in brain amyloid burden, as evidenced by positron emission tomography (PET) imaging. The analysis conducted following the specified protocol by Dhadda et al. (2022) demonstrated favourable outcomes for all endpoints and statistical models considered, with the ADCOMS analysis, as outlined in the protocol, indicating a 29.7% slower decline than placebo at the 18-month mark.

The **Clarity AD** (NCT03887455) study was an 18-month, multicentre, double-blind, placebo-controlled, parallel-group phase 3 trial with an open-label extension (OLE) in participants with early Alzheimer's disease (AD). The results were published by van Dyck et al. under "Lecanemab in Early Alzheimer's Disease". All 1795 eligible participants were randomly assigned to one of two treatment groups (placebo and lecanemab 10 mg/kg biweekly) in a 1:1 ratio. The primary endpoint was the change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB). Secondary endpoints included changes in amyloid burden as observed on positron emission tomography (PET), scores on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14), the Alzheimer's Disease Composite Score (ADCOMS), and scores on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL). The results demonstrated that Lecanemab diminished markers of amyloid in patients with early-stage Alzheimer's disease (AD), resulting in a moderately reduced decline in cognitive and functional measures when compared to the placebo group at the 18-month mark. Specifically, there was a 27% decline in the CDR-SB, a 26% slowed loss of cognition on ADAS-Cog14, and a 37% slowed loss of function on the ADCS-MCI-ADL. However, adverse events were observed, with lecanemab administration resulting in infusion-related reactions in

26.4% of participants and amyloid-related imaging abnormalities with oedema or effusions in 12.6%. (van Dyck et al., 2023)

The **AHEAD A3–45** Trial (NCT04468659) has been designed to investigate whether clearance of aggregated forms of Aβ caused by lecanemab administration in participants with preclinical AD and in participants with early preclinical AD is efficacious in slowing the progression of the AD pathophysiological continuum and onset of cognitive decline. (Rafii et al. 2023) The study utilises innovative approaches to enrich the sample with individuals with elevated brain amyloid.

The AHEAD A3–45 Study comprises two sister trials, A3 and A45, conducted in cognitively unimpaired individuals aged 55 to 80. The specific dosing regimens are tailored to baseline brain amyloid levels as determined by screening positron emission tomography (PET) scans. The A3 trial is a phase 2 trial with PET imaging endpoints designed for individuals with intermediate amyloid levels. The A45 trial is a phase 3 trial with a cognitive composite primary endpoint for individuals with elevated amyloid levels. The two trials are being conducted under a single protocol, with a shared screening process and a standard schedule of assessments. This trial is projected to end in 2027 and will provide helpful information about lecanemab as a potential preventative therapy for AD. (Vitek et al. 2024)

Efficacy in meta-analyses

The findings of the meta-analysis conducted by Abdelazim et al. (2024) indicated a statistically significant reduction in ADCOMS, CDR-SB and ADAS-cog14 scores when lecanemab was administered at a dosage of 10 mg/kg in comparison to a placebo. The efficacy of lecanemab was corroborated by narrow confidence intervals and the absence of significant heterogeneity. Although the incidence of treatment-emergent adverse events (TEAEs) did not differ significantly between the lecanemab and placebo groups, the elevated risks of ARIA-E and ARIA-H associated with lecanemab highlight the necessity for rigorous safety surveillance in clinical practice. Notwithstanding the drug's efficacy, the study underscores the necessity for a balanced assessment of the benefits and potential risks associated with lecanemab, thereby offering invaluable insights for clinicians evaluating its use in individuals with Alzheimer's disease.

The meta-analysis conducted by Wu et al. (2023) demonstrated statistically significant improvements in clinical outcomes during lecanemab treatment, including the CDR-SB, ADCS-ADL-MCI, ADCOMS scales, and the ADAS-Cog test. Furthermore, a substantial

reduction in amyloid PET SUVr was confirmed. Statistically significant changes in biomarker levels were observed, with increased levels of CSF Aβ1-42 and plasma Aβ42/40 ratio, as well as a decrease in CSF P-Tau, CSF T-Tau and plasma p-tau181.

The meta-analysis conducted by Qiao et al. (2023) is based on reliable data from all included studies, comprising 2,262 participants. The analysis revealed a statistically significant improvement in cognitive outcomes associated with early Alzheimer's disease (AD), as measured by the CDR-SB, ADCOMS, and ADAS-Cog scales. The statistically substantial cognitive benefits of monoclonal antibodies revealed in this meta-analysis were particularly noteworthy because most original studies did not reach significance on ADAS-Cog. No significant difference was observed in SUVr ($p = 0.38$) in the lecanemab group, with a statistically significant heterogeneity ($I^2 = 97\%$, $p < 0.00001$). Furthermore, the load of PET amyloid protein in the lecanemab group was significantly increased, exhibiting pronounced heterogeneity ($I^2 = 98\%$, $p < 0.00001$).

Safety Profile and Side Effects

During the clinical trials, patients who received lecanemab demonstrated a spectrum of adverse effects, most classified as mild to moderate in severity. (Chowdhury & Chowdhury, 2023) The Clarity AD trial demonstrated that lecanemab was generally well-tolerated, with no deaths directly attributable to its use. (van Dyck et al., 2021) In the Core 201 Study, during the Core + OLE phases, adverse events in the lecanemab group occurred in >10% of patients. The most common were infusion-related reactions (24.5%), ARIA with hemosiderin deposits (ARIA-H), microhemorrhages (16.0%), SARS-CoV-2 infection (14.7%), ARIA with oedema (ARIA-E; 13.6%), and headache (10.3%). (Swanson et al., 2021; Honig et al., 2024)

- **Infusion-Related Reactions:** Symptoms include headache, nausea, and dizziness during or shortly after the infusion.
- **Amyloid-Related Imaging Abnormalities (ARIA):** Specifically, ARIA-E (vasogenic oedema) and ARIA-H (hemosiderin deposits, microhemorrhages, microhemorrhages) can be monitored through regular imaging studies, typically on magnetic resonance imaging (MRI) sequences (Honig et al., 2023). The most prevalent symptoms of ARIA are headaches, confusion, visual alterations, dizziness, nausea, gait impairment, seizures, encephalopathy, stupor, and focal neurological deficits. (Honig et al., 2023) The Phase 2 Study 201 trial (NCT01767311) demonstrated that the incidence of ARIA-E was dose-dependent, occurring with greater frequency in the highest doses. The

overall incidence of ARIA-E was low (less than 10%), with less than 3% of cases presenting with symptoms. The majority of ARIA-E cases were asymptomatic, with a mild to moderate severity, and manifested within the first three months. (Swanson et al., 2021) The elevated prevalence of ARIA-A and ARIA-H in the lecanemab group relative to the placebo cohort was subsequently validated in further meta-analyses (Abdelazim et al., 2024; Wu et al., 2023; Qiao et al., 2023). The occurrence of ARIA-E was correlated with the maximum serum concentration of lecanemab, with a higher incidence observed in individuals homozygous for the apolipoprotein E4 (ApoE4) allele. (Honig et al., 2023) However, the exact pathophysiology underlying ARIA remains uncertain. Given the elevated risk of ARIA, symptomatic ARIA, and recurrent ARIA among APOE4 carriers (particularly homozygotes), it is recommended that APOE genotyping be performed on all treatment candidates before initiating lecanemab therapy. (Cummings et al., 2023)

- **Cerebral Macrohemorrhage**: It is more probable that a significant central nervous system event, frequently accompanied by enduring neurological deficits, will occur when anticoagulants are administered to patients with pre-existing microbleeds or amyloid beta-related angiitis (ABRA) or cerebral amyloid angiopathy-related inflammation (CAA-ri). (Cummings et al., 2023)

Among the aforementioned adverse effects, some gastrointestinal and neurological symptoms have been documented, including nausea, vomiting, diarrhoea, anorexia, dizziness, depression and headache. (Qiao et al. 2023)

Further research with larger cohorts is required to validate these findings and elucidate the clinical significance of the observed protective effect, which pertains to reducing the risk or severity of adverse outcomes associated with a particular intervention or factor.

Comparison of Lecanemab and Traditional Alzheimer's Therapies

Conventional therapeutic agents, such as cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists, are designed to provide symptomatic alleviation. They are generally well-tolerated but may induce adverse effects, including gastrointestinal disturbances, insomnia, and muscle cramps. These potential side effects could impact patient compliance. In contrast, the adverse effects associated with lecanemab are more closely related to its mechanism of action, which primarily targets amyloid-beta plaques intending to slow cognitive decline.

The following table provides a comparison between the two therapies in question.

Aspect	Leqembi® (Lecanemab)	Traditional Alzheimer's Treatments
Primary Purpose	Disease modification by reducing amyloid-beta plaques	Symptomatic relief of cognitive and behavioral symptoms
Mechanism	Monoclonal antibody-mediated clearance	Neurotransmitter modulation
Personalization	Genetic profiling (ApoE status)	General population
Primary Side Effects	Infusion-related reactions, ARIA	Gastrointestinal issues, sleep disturbances (insomnia), muscle cramps
Long-Term Safety	Uncertain	Varies by medication, often requires ongoing management
Monitoring Requirements	Regular imaging studies	Routine clinical assessments
Long-Term Impact	Potential to slow disease progression	Temporary symptomatic relief
	Quality of Life Metric	
Daily Living Activities	Maintains independence longer	Limited impact, primarily symptomatic relief
Cognitive Function	Slows decline, improves memory retention	Temporary improvement, gradual decline continues

Table 1. Chosen differences between therapies with lecanemab and traditional Alzheimer's disease medications.

While Leqembi® has some safety concerns, its benefits in altering the course of the disease offer a significant advantage over traditional therapies that primarily treat symptoms.

Administration and Accessibility

Lecanemab is administered via intravenous infusion every other week, typically in a clinical setting, which differs from the majority of conventional Alzheimer's medications, which are available in oral formulations and can be self-administered. The dosage is adjusted

according to the patient's weight, with 10 milligrams per kilogram of body weight administered. (Cummings, 2023)

The Alzheimer's Disease and Related Disorders Therapeutics Work Group (ADRD TWG) developed the appropriate use recommendations (AUR) for lecanemab. (Cummings et al., 2023)

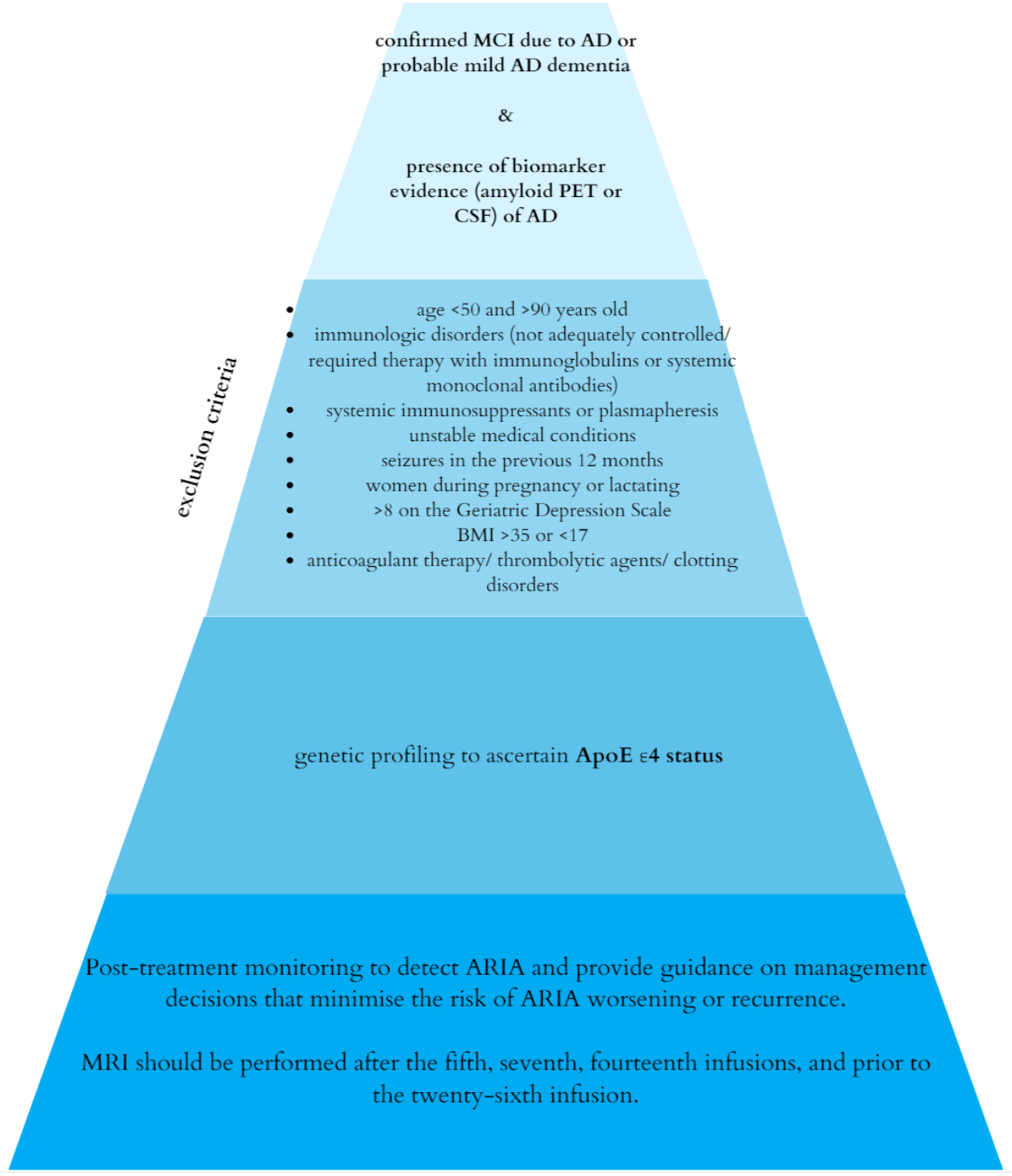

Figure 1. Scheme illustrating the following steps (read from top to bottom) of appropriate use recommendations (AUR) based on Cummings et al. (2023).

In patients presenting with ARIA-E and ARIA-H, dosing recommendations should be adjusted on a case-by-case basis, taking into account the specific clinical symptoms, the underlying type of ARIA, and the severity of the radiographic findings. (Chowdhury & Chowdhury, 2023)

Quality of Life Metrics

The assessment of the impact of Leqembi® on quality of life necessitates utilising a range of metrics that extend beyond the domain of clinical symptoms. Examining these metrics provides a comprehensive understanding of the drug's benefits. These metrics demonstrate that Leqembi® addresses not only the biological aspects of Alzheimer's disease but also significantly enhances the overall quality of life for patients and their families. Lecanemab was associated with relative preservation of health-related quality of life (HRQoL) and a lesser increase in caregiver burden. Benefits were observed consistently across different quality-of-life scales and within scale subdomains. (Cohen et al., 2023)

Future Directions in Alzheimer's Research

The approval and implementation of Leqembi ® (lecanemab) marks a pivotal moment in Alzheimer's research. Another potential avenue for advancement is the treatment of patients with Alzheimer's disease to address the underlying cause of the condition and expand the range of possible therapeutic targets. Further investigation may be directed towards the aggregation of Tau proteins, neuroinflammation and its role in the modulation of the brain's inflammatory response associated with neurodegeneration, as well as the preservation of synaptic health. The latter has been linked to enhanced synaptic plasticity and increased connectivity, contributing to improved cognitive resilience. These avenues represent an integrated and comprehensive approach to the treatment of Alzheimer's disease from a multitude of biological perspectives. This approach may ultimately result in developing combination therapies that demonstrate enhanced efficacy.

The CHMP's recommendation for Leqembi® use in ApoE ε4 non-carriers or heterozygotes underscores the significance of personalised medicine in Alzheimer's treatment. It seems likely that future research will concentrate on genetic profiling to identify genetic markers and develop tailored therapies. Moreover, the possibility of predictive analytics based on genetic data to predict disease progression and tailor intervention strategies may emerge.

The implementation of personalised medicine may not only enhance the efficacy of treatment but also mitigate adverse effects.

Furthermore, technological advancements will facilitate and enhance the future exploration of Alzheimer's. To illustrate, using artificial intelligence and machine learning facilitates the enhancement of data analysis, pattern recognition, and predictive modelling, thereby enabling the uncovering of novel insights into Alzheimer's pathology. The application of advanced imaging techniques has enhanced the resolution and accuracy of brain imaging, thereby facilitating the detection of early signs of neurodegeneration. Genomic sequencing has facilitated comprehensive genetic analyses, which in turn have facilitated the identification of novel therapeutic targets and the understanding of disease mechanisms at a molecular level. These technologies have accelerated research and facilitated the implementation of more precise and targeted interventions, thereby creating an environment conducive to discovering innovative treatments for Alzheimer's disease.

It is of the utmost importance that efforts to address Alzheimer's disease are conducted in a coordinated manner on a global scale. In the future, there may be an emphasis on the importance of collaborative research initiatives that bring together scientists, healthcare providers, and policymakers to share data and resources, standardise protocols, or promote public-private partnerships. Additionally, these collaborative efforts must be undertaken in order to overcome the complex challenges posed by Alzheimer's disease and achieve meaningful progress in its treatment and prevention.

Discussion

Four monoclonal IgG1 antibodies targeting Aβ are currently in late-phase clinical development: lecanemab, aducanumab, gantenerumab, and donanemab. Lecanemab is distinguished from gantenerumab and aducanumab by its tenfold stronger binding to protofibrils than fibrils (Söderberg et al., 2022). The disparate binding profiles may elucidate the diverging clinical outcomes observed for these antibodies concerning efficacy and adverse effects.

The synthesis of data from high-dose trials of three available antibodies (aducanumab, lecanemab, and donanemab) confirms that these drugs exert a statistically significant but slight clinical effect in patients with early AD after 18 months. However, an analysis of the safety data indicates that these drugs are associated with a significant risk of ARIA, which can be severe and may have long-term consequences. (Villain et al., 2022) Of the four antibodies previously mentioned, lecanemab displays the most favourable safety profile, with a 10%

occurrence of ARIA-H, which is approximately threefold less than the occurrence observed in aducanumab, gantenerumab, and donanemab. (Söderberg et al., 2022).

The mechanism of action of lecanemab has implications for both the therapeutic potential of the drug and the clinical decisions that must be made regarding patient selection and treatment protocols. Guaranteeing patient safety may require a dedicated member of staff who is available to oversee the numerous steps and interactions involved in the treatment process. These steps encompass logistics related to intravenous (IV) administration, the timing of infusions every two weeks, coordinating follow-up magnetic resonance imaging (MRI) scans on a conservative schedule, and ensuring that the MRI is read and reviewed before the next infusion. (Knopmann & Hershey, 2023)

The Committee for Medicinal Products for Human Use (CHMP) 's favourable opinion of recommending granting marketing authorisation for Leqembi® has been met with controversy. Some papers have argued that the 18-month time interval is insufficient to achieve or appreciate the maximal benefits and evaluate the risk-benefit ratio of this class of drugs in early Alzheimer's disease (AD). (Villain et al., 2022; Kurkinen, 2024; Knopmann & Hershey, 2023). Furthermore, the complex and multifaceted nature of Alzheimer's disease (AD) has been emphasised, and the necessity for a more comprehensive research perspective that extends beyond the simplistic disease model proposed by the Amyloid Cascade Hypothesis (ACH) has been highlighted. (Granzotto & Sensi, 2024)

The existing literature highlights several negative aspects that require further investigation through real-life research. Kurkinen (2024) draws attention to less optimistic outcomes from van Dyck et al. (2023), namely that the 18-month trial did not demonstrate a slowing of cognitive decline in women, who are at a twofold increased risk of AD compared to men, following treatment with lecanemab. Moreover, lecanemab did not demonstrate efficacy in slowing cognitive decline in APOE4 carriers, who constitute 60–75% of AD patients. Conversely, the treatment accelerated cognitive decline in participants with two APOE4 genes. (Kurkinen, 2024)

Moreover, a comprehensive Bayesian re-analysis of the lecanemab phase III clinical trial (Clarity AD) has demonstrated an absence of evidence substantiating the efficacy of Lecanemab compared to placebo. This analysis has also revealed an inability to corroborate the statistically significant impact of Lecanemab. (Costa et al., 2023)

The authors of the meta-analysis by Qiao et al. (2023) have identified a further issue: lecanemab and other anti-amyloid drugs have not been evaluated adequately since each research variable is different in key biomarkers, which makes it impossible to compare them. Moreover,

the authors highlight the issue of publication bias, noting that negative results and non-statistical data are often challenging to publish, resulting in their exclusion from meta-analyses. (Qiao et al., 2023)

The open-label long-term extension observations from the lecanemab trials, which emerge three or four years after the commencement of therapy, are anticipated to prove pivotal to our understanding of the benefits. (Knopmann & Hershey, 2023)

In the context of the ongoing controversy, the results of simulation models appear to indicate the potential benefits of lecanemab treatment. The initial model proposed by Tahami Monfared et al. (2022) showed that lecanemab could potentially enhance long-term health outcomes (an increase of 0.61 QALYs) and reduce the costs associated with formal and informal care. Moreover, Tahami Monfared et al. (2022) utilised a disease simulation model to forecast the long-term clinical outcomes of lecanemab for patients with early-stage Alzheimer's disease (AD). The results indicated that the treatment was predicted to decelerate the rate of disease progression, resulting in an extended duration of mild cognitive impairment (MCI) due to AD and AD dementia and a shortened duration in moderate and severe AD dementia. Moreover, the model demonstrated a diminished probability of necessitating institutional care at any point throughout the patient's lifespan in those who received lecanemab treatment.

Conclusions

This paper examines the clinical trials that have established the efficacy of lecanemab in treating early Alzheimer's disease and provides a comprehensive analysis of the drug's tolerability and management of adverse effects.

It is of the utmost importance that care partners and family members of patients considering treatment with lecanemab possess a comprehensive understanding of the potential benefits, as well as the probability of ARIA and its associated consequences, the possibility of infusion reactions, the necessity for twice-monthly intravenous infusions, and the requirement for MRI scans during the initial year of therapy. It is recommended that patients interested in treatment with lecanemab be informed that APOE genotyping is advised and that confirmation of amyloid pathology in the brain be conducted through either amyloid PET or CSF studies. Moreover, an MRI scan performed within the past 12 months is required to ascertain that the patient has no pathological conditions incompatible with lecanemab therapy.

Furthermore, it is essential to obtain long-term safety data to comprehend the implications of prolonged lecanemab utilisation. The monitoring of patients for up to three years revealed a consistent pattern of adverse effects, which in turn facilitated the formulation of

proactive management strategies for infusion-related reactions and ARIA. These findings suggest that, with appropriate monitoring and management, lecanemab can be safely integrated into long-term treatment plans for Alzheimer's patients. Nevertheless, further research and accumulating real-world data will be necessary to substantiate its long-term benefits and establish its role in managing this debilitating condition.

In conclusion, the narrative review not only highlights the significant advancements brought by innovative targeted treatment offered with lecanemab but also outlines the promising future directions that will continue to drive progress in Alzheimer's research, offering a promising prospect for modifying the disease course rather than merely alleviating symptoms. Furthermore, the study identifies existing knowledge gaps concerning the long-term efficacy and safety of the treatment regimen with this novel pharmaceutical agent. By prioritising disease modification and integrating principles of personalised medicine, lecanemab represents a pioneering approach within the field of Alzheimer's therapy. As we advance, the integration of personalised medicine, technological innovations and collaborative efforts may be a crucial element in our endeavour to manage neurodegenerative diseases.

Authors' contributions statement

Conceptualization: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
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