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Kisunla (Donanemab): A Novel Breakthrough Illuminating a Path to Better Alzheimer's Outcomes

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Abstract

Background: *Alzheimer's disease (AD) is a progressive neurodegenerative condition marked by cognitive decline, memory loss, and loss of independence. Despite decades of extensive research, disease-modifying treatments have been limited in success. Recent therapeutic advancements have led to the development of monoclonal antibodies targeting amyloid-beta (Aβ) plaques, particularly the pyroglutamate-modified variant, a key pathological hallmark of AD.* ***Objectives:*** *This review aims to explore the therapeutic potential of Donanemab (Kisunla), a novel monoclonal antibody, in slowing disease progression in early symptomatic AD. The study also seeks to assess its clinical efficacy, safety profile, and regulatory journey, while comparing it to other amyloid-targeting therapies.* ***Methodology:*** *A comprehensive analysis of published literature and clinical trial data was conducted, with a focus on the TRAILBLAZER-ALZ clinical programs. Key inclusion and exclusion criteria of the studies were assessed, and trial outcomes related to cognitive performance, amyloid clearance, and safety (especially amyloid-related imaging abnormalities-ARIA) were reviewed. Comparisons were drawn with other similar agents to evaluate relative effectiveness.* ***Results:*** *Donanemab demonstrated significant efficacy in reducing amyloid burden and slowing cognitive decline in early symptomatic patients. The TRAILBLAZER-ALZ trials presented strong clinical evidence for amyloid clearance and improved patient outcomes. However, safety concerns, like ARIA, were reported and carefully monitored. Regulatory agencies acknowledged the potential of Donanemab, granting accelerated approvals based on trial outcomes.* ***Conclusion:*** *Donanemab represents a promising advancement in AD therapeutics, potentially altering the treatment landscape through disease modification. Its early intervention approach and favorable efficacy outcomes indicate a hopeful shift in Alzheimer's management, though long-term safety and comparative effectiveness require further evaluation.*

Keywords: Alzheimer's disease, amyloid-beta, disease-modifying therapy, Donanemab, Kisunla, monoclonal antibody

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INTRODUCTION

Alzheimer's disease (AD) is the most prevalent dementia, causing 60–70% of all dementia cases, and although its cause is not fully understood, the disease is a fast-growing public health problem, being the most common form of dementia presently. It is estimated that more than 7.2 million people in the United States aged 65 and over will live with AD, and the majority will be women. It is estimated that by 2050, the world will be home to over 150 million victims of the disease mainly brought about by an aging population. AD has become one of the leading causes of death among the elderly, and its burden in terms of both disability-adjusted life years and mortality has decreased tremendously over the past few decades [1]. The financial impact is also

excruciating, as the U.S. is expected to reach $384 billion in costs dealing with care in 2025, with the figures expected to increase almost as high as $1 trillion by it is observed that the QR code is simply positioned, i.e., it is placed and not simply put. The informal care provided by almost 12 million citizens of the United States is an added burden, with more than 19 billion unpaid care hours supplied each year. Even though this is burdensome, there exist limited disease-modifying therapies. Most of the existing treatments provide symptomatic improvements without arresting the disease. There also exist difficulties in early detection given the different dependence on invasive/high-cost tests, and the patient usually faces complicated comorbid and treatment plans. Inequality in care can be seen, especially among ethnical minorities and women. The main processes of AD pathology are the aggregation of the amyloid-beta (Aβ) peptides, as a result of which the so-called Aβ plaques are formed, which interfere with the interaction between neurons and mediate the development of tau pathology and the neuroinflammatory reaction. Although the role of A beta in the development of the pathogenesis of the disease is undeniable, the specific pathogenic mechanisms and the mechanism of its interaction with other pathogenic processes are not fully clarified, which is currently the subject of scientists. In general, Alzheimer still represents major diagnostic, therapeutic, and socio-economic issues, and Aβ still represents an initial target of intervention and investigation [2].

Donanemab (Kisunla), developed by Eli Lilly and Company, is a monoclonal antibody that the FDA authorized in July 2024 to treat patients with mild cognitive impairment or mild dementia due to AD in patients who have been proven to have amyloid pathology. In contrast to previous symptomatic therapies, Donanemab attacks the pathology itself by binding to nitrated-pyroglutamate-modified *A* amyloid-beta (N3pGlu A % Ega), which forms part of amyloid plaques. This helps to evoke clearance of the plaque by activating microglia, which would modify the course of the disease. *Clinical trials (especially the* TRAILBLAZER-ALZ series) have shown that Donanemab can reduce the burden of amyloid by up to 50% and slow down cognitive impairment. Of note, almost half of the patients in these trials have been on treatment within 1 year, which makes Donanemab the first anti-amyloid backbone of a time-limited treatment regimen, as opposed to lifelong dosing, depending on the clearance of the plaques. Supplied through monthly infusions, it is convenient, and its safety profile is overall tolerable, with amyloid-related imaging abnormalities (ARIA) and infusion-related reactions being the key observables to monitor. This review seeks to testify to a rigorous analysis of the scientific rationale, trial-derived evidence, safety, and future position of Donanemab in contemporary AD therapy as well as the practical aspects of cost, access, regulatory affairs, and the position against other upcoming drugs [3].

PATHOPHYSIOLOGY OF AD

AD is an irreversible neurodegenerative disorder characterized by the loss of neurons and synapses that takes place in the cerebral cortex and certain regions of the subcortex. This causes cerebral loss and memory loss as well as thinking deficiency. It is predominantly caused by two pathological hallmarks, as shown in Figure 1, which are extracellular amyloid-beta (Abeta) plaques and intracellular neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau proteins. The amyloid cascade hypothesis claims that the formation of A is the result of the process which starts with the presence of A and begins with the formation of Ab42. Such misfolded forms are due to the cleavage of amyloid precursor protein (APP) by β- and γ-secretase enzymes, producing toxic oligomers and plaques. This cascade enhances the hyperphosphorylation of tau, thus stimulates glial cells (astrocyte and microglia), impairs synaptic proteins and generates neuronal injury. Mutations of such genes as APP and proteins presenilins (PSEN1/2) are also associated with early-onset familial AD evidencing the pivotal role of A beta in the development of the disease [4].

Also, in AD, tau protein is hyperphosphorylated and forms NFTs that have destabilized microtubules and impaired axonal transport, and represent neuronal death. Inflammation and oxidative stress, in turn, worsen brain damage with the pro-inflammatory glial cells secreting cytotoxic cytokines and ROS.

AD normally runs through asymptomatic to mild cognitive impairment and dementia. The designated biomarkers in the form of lower Abeta 42 in blood composition, higher phosphorylated tau in cerebrospinal fluid, and neuroimages characterized by atrophy on the hippocampus are used to track

the evolution of the disease. There are also other factors that further contribute to the pathogenesis of AD, which include cholinergic deficits, glutamate-TIM timed excitotoxicity, mitochondrial function, blood–brain barrier, and alteration of flora in gut. All these mechanisms interrelate and explain the multifactorial character of AD and the significance of biomarker-driven diagnosis and monitoring [5].

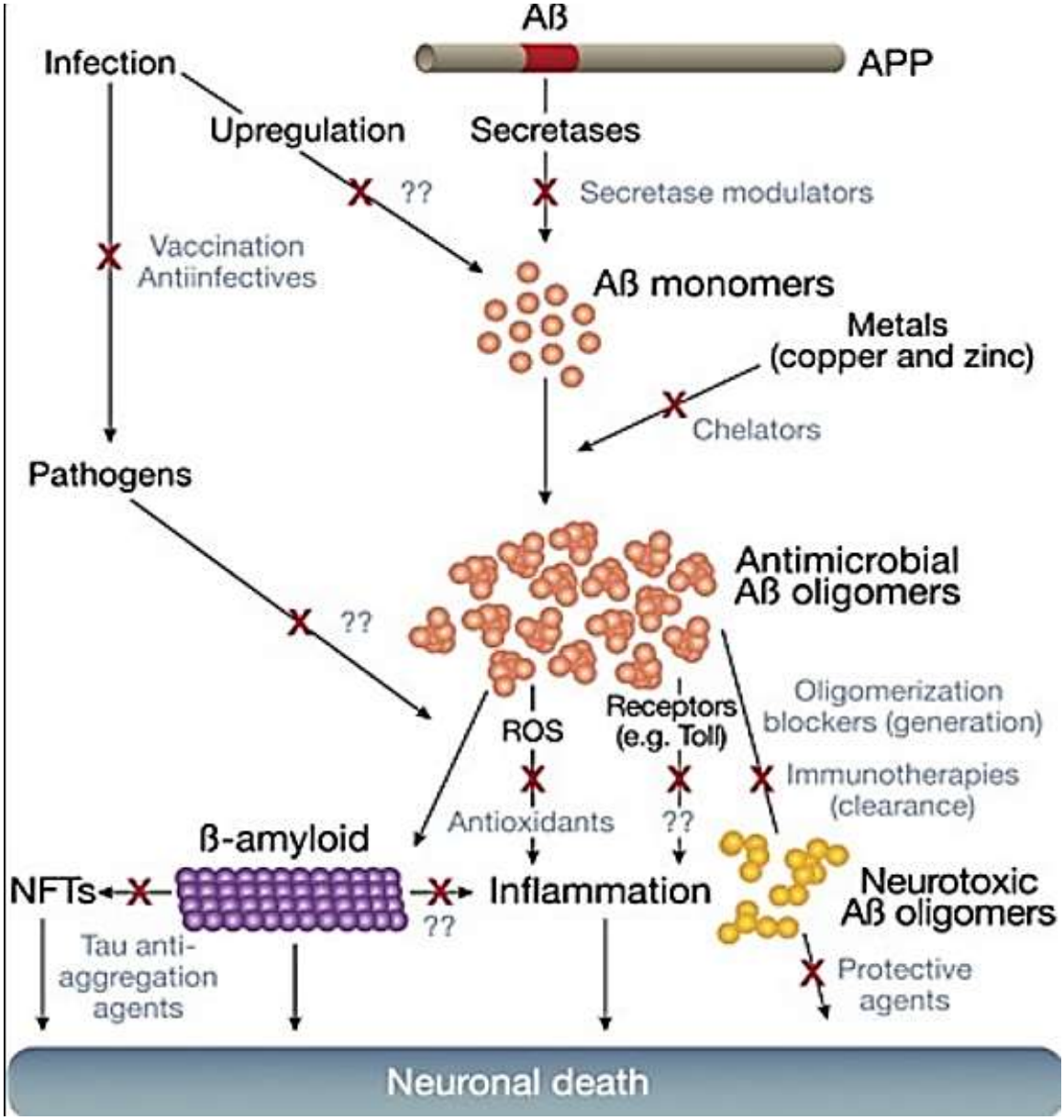

Figure 1. Therapeutic targets in the amyloid-beta cascade and Alzheimer's disease pathogenesis.

MECHANISM OF ACTION

- *Pathology of AD:* One of the primary pathophysiological features of AD is the accumulation of amyloid plaques and NFTs. Beta (b)-amyloid peptides result in the formation of amyloid plaques, and hyperphosphorylated tau proteins result in the formation of NFTs. Along with cognitive deterioration and synaptic incompetence, in AD, these changes occur.
- *The Amyloid Cascade Hypothesis:* The amyloid cascade hypothesis is a theory in which the coincidence of amyloid beta (A Amyloid) is suggested as one of the leading occurrences before the establishment of AD. Based on this hypothesis, a pathological accumulation of neurotransmitter tau, caused by the acquisition of A beta aggregates, leads to neurodegeneration and cognitive decline. The most essential

stage in the process is the reason, however, which consists of the calcium balance disturbance, leading to hyperphosphorylation of tau. The phosphorylated tau proteins are later seen to form paired helical filaments, which are later united to form what are known as NFTs (Figure 2).

- *Aβ Generation and Aggregation*: Breakdown of the APP results in A peptide (A beta). In the absence of disease, APP is cleaved into another nontoxic cleavage product by an enzyme called α-secretase to yield a solute-free molecule, sAPPalpha. But it is also possible that APP is cleaved by another enzyme known as 2-secretase (or BACE1) present in AD, which produces a different fragment known as sAPP b and a piece termed C99. Then, γ-secretase cleaves C99, releasing A peptides. The length of these peptides may vary, but the most prevalent of these is A81wees140, with the more harmful and aggregating being A81wees142. Peptides begin to aggregate, building oligomers, fibrils, and finally, plaques-one of the hallmarks of AD.
- *Pyroglutamate Amyloid-beta (Aβp3-42):* Abeta p3-42 is the most dangerous form of A beta. This is derived when the peptide is cut at N-terminus, and a residue of glutamate is found on the 3rd position. The process of modifying glutamate is pyroglutamylation. This solidifies the resulting A8p3-42 peptide into a very sticky substance and is more prone to aggregation. It does not easily break down in the body, and hence, it is toxic enough to add to what is being destroyed in the brain during AD [6].
- *Donanemab (N3pG) and Its Mechanism of Action:* Donanemab-A monoclonal antibody that is specifically aimed at the modified version of Aβ that is deposited in the amyloid plaques in the form AβpE3-42 (or Aβ3(pE)-42). The clearance of amyloid plaques aids in binding Aβp3-42 to amyloid plaques and is successful when the microglia immune cell is involved. The urgency of the given strategy has been deemed to be a matter of pressing issues as Donanemab attaches to more stable plaques and helps to eliminate them, whereas the A-beta takes a soluble form in many cases, which therefore, fails to indicate the presence of plaques [6].
- *Donanemab's Role in Treating AD:* Donanemab is meant to neutralize the damage that Aβ accumulation in the brain causes. It is a humanized IgG1 monoclonal antibody that targets the Aβp3-42 and facilitates the removal of amyloid plaques from the brain. By removing these plaques, Donanemab may stop or even reverse the progression of AD and stimulate symptoms by dissolving the toxic accumulation of Aβ in the brain [6].

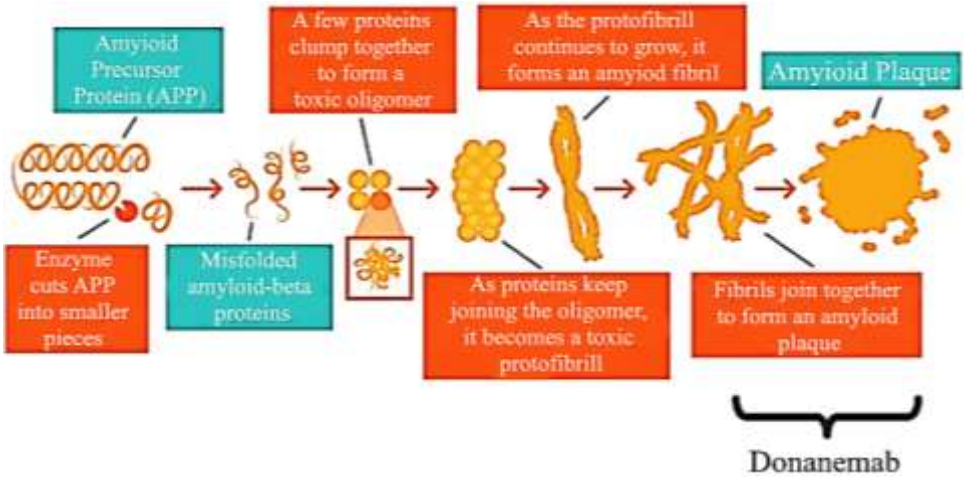

Figure 2. Formation of amyloid plaques from APP and the therapeutic role of Donanemab clinical development and trial landscape.

PHASE I/II TRIALS

Phase I/II clinical trials are an important stepping stone toward determining efficacy of new therapies whose main aim of consideration is usually shown in Table 1. The establishment of safety, pharmacokinetics, potential evidence of efficacy, and appropriate dosing regimen. Small cohorts (healthy volunteers, or study patients) are deployed during Phase I to evaluate the safety profile, define adverse events, the maximum tolerated dose (MTD), with carefully preset protocols of dose escalation.

Experiments that fall under the pharmacokinetic category that are carried out in this phase assess the absorption, distribution, breakdown, and excretion of drugs, producing highly important information such as peak plasma concentration, clearance, and half-life. Upon the determination of a safe dose, Phase II trials are extended to patients with the target condition to determine preliminary effectiveness by way of endpoints that may include tumor response rates, alterations in biomarkers, or patient-reported outcomes. Expansion of doses during this stage aids in confirmation of safety and optimization of doses in future studies. Adaptive approaches and advanced statistics models that enhance assessments of dose-limiting toxicity and determination of the recommended Phase II dose (RP2 D) are frequently integrated in modern designs, which make the progression to subsequent phases of the trials more efficient and ethically justified [7].

Table 1. Comparison of phase I and phase II clinical trial characteristics.

Aspect	Phase I Focus	Phase II Focus
Primary Goal	Safety, PK, dose/MTD identification	Preliminary efficacy, safety, dose refinement.
Population	Small, Healthy/ selected patients	Patients with target disease.
Dose Escalation	Sequential, small cohorts	Expansion cohorts at selected dose.
Efficacy Assessment	Early/ biomarker signals at best	Primary efficacy endpoints.
Safety Monitoring	Continuous, focus on DLT	Serious & common adverse events.

TRAILBLAZER-ALZ AND SUBSEQUENT TRIALS

The TRAILBLAZER-ALZ clinical trial program has determined the efficacy and safety of Donanemab (anti-amyloid monoclonal antibody) against early symptomatic AD. In a Phase 2 trial and Phase 3 trial, Donanemab demonstrated a pronounced cognitive and functional stability – a 32–35% reduction in cognitive and functional deceleration on tests, such as iADRS and CDR-SB, corresponding to a 5–6-month delay in the rate at which the disease progressed. The participants are 60–85 years old and biomarkers with established amyloid and tau pathology were treated with intravenous infusions 4 weeks apart and lasted up to 76 weeks. Amyloid PET showed clearance of plaque with up to 80% of patients becoming PET-negative by week 76. An early stop discretionary to treatment at a threshold level of amyloid (<24.1 Centiloids) and follow-up revealed most were below this amyloid level even after termination [8].

The safety results noted ARIA as being the most frequent issue, in particular ARIA-E and ARIA-H, with increased risk in APOE 4 carriers. Infusion-related reactions were present in a small proportion and withdrawal of treatment because of adverse events was greater among Donanemab recipients compared with placebo. Additional trials (TRAILBLAZER-ALZ 3-6) are underway to examine the effect of Donanemab in preclinical patients, dosing approaches that would minimize the likelihood of causing ARIA, and placebo-controlled comparisons of the effects of Donanemab relative to other treatments such as aducanumab. It is recommended that long-term monitoring should be done in monitoring amyloid reaccumulation and guide re-retreatment. In general, Donanemab has a meaningful clinical effect on the progression of Alzheimer, and treatment options depend on each patient in terms of PET scan imaging and safety status [9, 10].

REGULATORY MILESTONES

On July 2, 2024, Donanemab, sold under the brand name Kisunla *(donanemab-azbt) was fully approved by the FDA to cure early symptomatic AD in adults whose amyloid is confirmed, who appear at the mild cognitive impairment or mild dementia period. The drug has been fast-tracked since it was first given Breakthrough Therapy labeling in June 2021, based on the favorable Phase 2 results, since it could dramatically improve on current therapies. Eli Lilly initially sought accelerated approval, but the FDA rejected this avenue in early 2023, stating there was insufficient long-term exposure data for enrolling in the pivotal trial. Rather, a conventional approval mechanism was used, which, eventually, was backed by complete efficacy and safety data of the third phase of the trial TRAILBLAZER-ALZ 2. On July 2025, label

adjustments to the drug included an amended titration schedule based on minimizing the occurrence of ARIA without compromising its clinical efficacy [11].

COMPARATIVE EFFECTIVENESS

Donanemab shows its remarkable disease-modifying effect in early Alzheimer's compared to conventional symptomatic medications in cholinesterase inhibitors (donepezil, rivastigmine, galantamine), and memantine. As opposed to conventional therapies, which result in modest cognitive improvement or stabilization without having an impact on the progressing nature of the disease, Donanemab has significantly reduced cognitive and functional deterioration by 32 and 35%, respectively, over 18 months of clinical trials. This should translate to a 4–7-month delay in the progression of the disease, and nearly half of the treated patients, to no clinical progression at 1 year; outcomes representing a significant improvement compared to placebo. Conversely, the effect sizes associated with the use of cholinesterase inhibitors and memantine are usually low and the interventions have no effect on the process of neurodegeneration [12].

Donanemab is more efficacious in terms of cognitive endpoints and amyloid clearance compared to other anti-amyloid monoclonal antibodies such as lecanemab and aducanumab. Nevertheless, it has an increased risk of ARIA, especially of ARIA-E so should be monitored closely by MRI, especially in people who are genetically at risk, including APOE ε4 carriers. However, the reality of targeted therapy is facing difficulties, such as specialized infrastructure, prohibitive costs of treatment, and the necessity to carefully select patients. Moreover, the generalizability issue and sparse long-term data continue to cause concern as to why more research is necessary to establish whether the observed effect would be long-lasting following termination of the treatment and extend our knowledge to other patient groups [13].

SAFETY AND TOLERABILITY

ARIA, an abnormal finding on CT or MRI, which includes ARIA-E (edema or effusion) and ARIA-H (microhemorrhages or superficial siderosis), are the main safety issues related to the administration of Donanemab and other related anti-amyloid in early AD. ARIA-E manifested in 24% of Donanemab-treated patients but only 2% of the placebo group, whereas ARIA-H manifested in 31% of the treated individuals against 13% of those on placebo in clinical trials. The majority of the ARIA-E occurred at moderate or mild levels and only 5–6% reported experiencing symptoms, such as headaches or confusion, with about 1.5% experiencing severe complications. These manifestations usually occurred during the initial three infusions and were usually self-limiting in the presence of good observation. Probably the most significant risks are carrying APOE e4, especially a homozygote, and the presence of abnormalities on the MRI scan before the trial started, a high baseline amyloid level, high blood pressure and the taking of anticlotting agents. On the contrary, use of antihypertensive treatment was linked to decreased occurrence of ARIA [14].

Lifelong ARIA management is an area that should incorporate well-selected patients, a screening baseline MRI, and repetitive imaging during the treatment. Before major infusions and in the case of neurological symptoms, MRI scans should be performed. Suspension of treatment is recommended only on a temporary basis during the case of mild ARIA-E without symptoms, until they resolve, but in persistent or severe cases, treatment should be stopped permanently. The same occurs with symptomatic or vast ARIA-H. In real-world practice, the use of this therapy requires caution due to greater risk in older people and in patients with other medical problems, groups that were underrepresented in trials. FDA administered a boxed warning to Donanemab because of the presence of rare but severe ARIA complications, together with fatal bleeding associated with misdiagnosis or underlying risk factors. In reducing the risk of ARIA, genetic screening, MRI review, patient education, and individualized dosing plans are important, particularly as that use becomes more widespread among different patients [15].

PATIENT SELECTION AND BIOMARKERS

Clinical and biomarker criteria were considerably narrow to guarantee candidates participating in Donanemab trials (with TRAILBLAZER-ALZ and its follow-ups) had early symptomatic AD with both amyloid and tau. The eligible patients were aged between 60 and 85 years; they had a clinically-

diagnosed mild cognitive impairment or mild dementia caused by Alzheimer (according to NIA-AA criteria), MMSE of the range 20–28 and were with a history of a gradual decline of memo during a time of at least 6 months recorded. Eligibility stipulated a partner in the study and the presence of amyloid detected on PET scans as well as pathology of tau at a range that was identified by tau PET scans. On the one hand, CSF biomarkers were sometimes used but, on the other hand, PET scans were the main method of diagnosis. APOE 4 genotype was also registered but not considered as an exclusion criterion since it is considered in the development of Alzheimer and the risk of ARIA. These trials are precision medicine style with the use of biomarker-based confirmation of AD, where people with less significant tau are more likely to be affected by such trials, as well as combining the aspects of risk management into genetic profiles, imaging data, and comorbidity. Current studies are working towards the inclusion of blood-mediated biomarkers to make them less invasive and to be able to use the biomarkers to dynamically select treatments on a personal level [16].

ECONOMIC AND ETHICAL CONSIDERATIONS

The new treatment of early AD, Donanemab, has significant economic and ethical issues despite its potential as a disease-modifying therapeutic. The treatment cost is more than $45,000, plus additional costs related to infusion, brain imagery, and safety monitoring, which makes it inaccessible to the masses and beyond the economic levels on a general scale. Its flexible dosing schedule, whereby treatment can be discontinued once adequate amyloid clearing has occurred, is a partial financial advantage over continuous therapies however, in practice, real-world experience has been limited by diagnostic and infrastructure needs. Reimbursement is still weak and patchy as insurers compare the high prices to relatively low clinical impact, usually a 4–7-month slowing down of progression. Ethically, there is a need to screen and diagnose early based on the use of biomarkers bringing forth the psychological effects, overdiagnosis, and unclear benefits particularly among asymptomatic persons. Moreover, the relatively low effectiveness must be weighed up with severe side effects, such as ARIA, which means challenging therapeutic decisions both on the side of patients and family. Fairness and access also come up as issues as prohibitive costs and logistics can easily result in disparities in health, especially with underrepresented and resource-limited groups. Also, concerns on how to allocate scarce healthcare resources to costly treatments with small benefits question the larger health policy. As policy, affordability, and the impact equity of care through research are debated further, the future of Donanemab in the treatment of Alzheimer and the way it is administered will be largely based on these factors and many more [17].

FUTURE DIRECTIONS AND RESEARCH GAPS

However, in the anticipation of future studies of Donanemab and the treatment of Alzheimer, there are some key areas of study that need to be addressed to help in establishing a better understanding and clinical outcomes. A key issue is assessing the long-term outcome following amyloid clearance. Many patients saw debris of amyloid plaques cleared after 76 weeks of Donanemab treatment and studies indicate that the plaques are unlikely to form significantly in a year once therapy stops. It is shown through modeling that the amyloid will require almost 4 years of reconstruction to regain prior values, and this may symbolize a sustainable advantage. Nonetheless, very little clinical data exist beyond 3 years, and further monitoring is expected to estimate whether the cognitive improvements will remain observable in the long-term and what intervals of time may require retreatment. The fact that complete clearing of amyloid is also associated with the reduced development of tau proteins that are directly connected with the loss of mental capabilities further demonstrates the significance of early interventions. Combination of Donanemab with anti-tau treatment is another promising methodology that is being studied because the combination of treating both amyloid and tau may have more effect on the pathology than any single treatment by itself [18].

The other major research requirement is better representation in clinical trials. The majority of Donanemab research conducted to date has been done in comparatively youthful, healthy subjects at the least advanced phases of Alzheimer where the outcomes cannot easily be generalized to the more extensive grievance base, such as older patients, those with different health problems, or racial and ethnic diversities. Future trials are broadening their study criteria to more closely mirror the populations

treated in the real world, and level out differences in access and outcomes to treatment. A number of ongoing trials are also evaluating new treatment approaches: TRAILBLAZER-ALZ 3 is testing whether early administration of Donanemab can prevent disease in amyloid-containing individuals (who are not yet symptomatic) and TRAILBLAZER-ALZ 4 is doing a direct comparison of Donanemab to another similar agent, aducanumab. Further studies (TRAILBLAZER-ALZ 5 and 6) will provide perfect dosing and monitoring approaches to enhance safety and efficacy. The durability and sustainability of the benefits are being measured in long-term follow-up extensions, as is the fact that Donanemab is and remains safe and effective over many years. Combined, these initiatives will enhance treatment, customize care and increase the effect of Donanemab in AD [19].

CONCLUSIONS

Donanemab (Kisunla) is a revolutionary breakthrough in the treatment option of early AD because it shows clinically and biologically relevant improvements via amyloid plaque clearance. With evidence available on TRAILBLAZER-ALZ clinical program, this monoclonal antibody can provide a significant delay in cognitive deterioration to a subset of rigorously chosen patients, and it should be considered as the disease-modifying medication and not a symptomatic medication. Although safety issues, including ARIA should be monitored adequately, the comprehensive safety-efficacy balance places Donanemab as a prospect in the landscape of early-stage AD treatment. Donanemab is a competitive or better anti-amyloid therapy agent regarding reducing amyloid and prolonging the progression of the disease when compared to other active concepts. Donanemab could open a door to more effective and specific methods of treating AD since the drug remains under trial with a higher population, longer follow-up, and possible combinations with anti-tau therapies. With more data becoming available, and with greater accessibility, Donanemab may play part in transforming the way we manage and even think about AD, making it a possibility of new hope and relief to the patients and their care-givers, who currently face this debilitating neurodegenerative disorder in the modern world.

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