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Review Article

New drugs for Alzheimer's disease: Aducanumab or Donanemab?

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ABSTRACT

The main pathological features of Alzheimer's disease (AD) include the cytotoxic extracellular accumulation of the amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles. The Aβ plaques are responsible for cholinergic dysfunction and dementia in AD patients. Immunoglobulin G (IgG) and Aβ form an immune complex that activates neuroglia, clearing Aβ from the brain. Various Aβ-based therapeutic strategies have been proposed to reduce Aβ production, inhibit Aβ aggregation, and increase Aβ clearance. New medicines, such as aducanumab and donanemab, which are human IgG1 monoclonal antibodies, reduce cognitive impairment in patients with AD by decreasing the amount of Aβ plaques. Despite the considerable advantages of these agents, some disadvantages have also been reported, including Aβ-related imaging abnormalities, anaphylaxis, high cost, and contradictory results. Moreover, donanemab has delivered contradictory outcomes in improving recognition and performance in AD. However, although not fully proven yet, fewer side effects are reported for donanemab compared to aducanumab. Therefore, this review aims to explore the research background, compare the mechanism of action, and understand the advantages and disadvantages of aducanumab and donanemab. As a result, these medicines with maximum effectiveness and safety, yet fewer side effects, could be developed for future treatment and references.

Keywords:
Amyloid-beta
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Introduction

Alzheimer's disease (AD), the most common type of dementia (Qiu et al., 2009), is characterized by alterations in personality, behavior, and cognitive impairment related to learning and memory (Bianchetti and Trabucchi 2001; Silva et al., 2019). Some risk factors for AD include old age (Hebert et al., 2010), family history of AD (Farrer et al., 1997), apolipoprotein E4 (ApoE4), obesity (Buchman et al., 2005), and depression (Sáiz-Vázquez et al., 2021). Various genetic and environmental factors, such as free radicals, head trauma, anoxia, and cholesterol levels in old age can be effective in

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cognitive impairments in AD with their effects on myelin development (Bartzokis 2004). Obesity can also increase the risk of AD by influencing glucose sensitivity and hyperinsulinemia (Tabassum et al., 2020). Family history, as well as the role of apolipoprotein E4 in AD, are related to genetic factors (Huang 2010; Xu et al., 2023). The cause of the increased risk of AD in people with a history of depression is not exactly clear, but some studies suggested that hippocampal atrophy after depression might be one of the factors that increase the risk of AD (Kim et al., 2021).

AD is characterized by intracellular neurofibrillary tangle (NFTs) formation, accumulation of extracellular amyloid beta (Aβ) plaques, and cholinergic system dysfunction (Rubio-Perez and Morillas-Ruiz 2012). The sequential cleavages of the Aβ precursor protein by β- and γ-secretase can lead to the production of toxic Aβ plaques in the brain (Refolo et al., 2000; Rubio-Perez and Morillas-Ruiz 2012; Weller and Budson 2018; Yang and Sun 2021). According to the Aβ hypothesis, Aβ plaques are considered responsible for neurodegeneration and dementia in AD. It is also associated with brain atrophy, synaptic dysfunction, and learning and memory impairment (Kim et al., 2020; Mo et al., 2017). Previous studies proposed the role of Aβ (Tolar et al., 2020) and also NFT which contains hyper-phosphorylated and aggregated tau (τ) protein (Rubio-Perez and Morillas-Ruiz 2012; van der Kant et al., 2020) in the pathogenesis of AD.

In animal studies, Aβ clearance has been linked to immune responses in the brain (Mo et al., 2017), and microglia and astrocytes have been introduced as mediator agents for neuroinflammation in AD (Van Eldik et al., 2016). The Aβ plaques aggregation proceeds the astrocyte and microglia aggregation and the activation and release of neuroinflammatory factors such as interleukins, complements, TGFα, 5LOX, and CRP. In addition, NFTs play a role in the release of CRP and TGFβ inflammatory markers in the brain (Hensley 2010). Peripheral immunoglobulin G (IgG) can also enter the brain bind to Aβ and generate an immune complex that can activate neuroglia to clear the brain from Aβ plaques (Mo et al., 2017). Overall, Aβ plaque aggregation, NFTs, and the subsequent stimulation of inflammatory responses by microglial and astrocytes start neurodegeneration (Rubio-Perez and Morillas-Ruiz 2012). However, in some cases, microglial activity decreased Aβ plaques in the brain (Frautschy et al., 1998).

So far, various medications, such as the inhibitors of cholinesterase enzyme (rivastigmine, galantamine, and donepezil) and NDMA receptor inhibitors (memantine) have been approved for AD, while none of them could successfully cure the disease. They could only alleviate the symptoms and slow disease progression (Hassan et al., 2022). Although Aβ has been proposed as the main cause of AD in the Aβ hypothesis, the effects of mentioned agents on Aβ are unknown. Therefore, it is necessary to develop new medicines that effectively affect β-Aβ production, aggregation, and deposition in the brain. Since 1992, many studies have focused on new anti-Aβ agents that can target, reduce, and eliminate Aβ in the brain. However, none of them have been approved by the United States Food and Drug Administration (FDA) (Vaz and Silvestre 2020).

To date, four types of anti-Aβ medications, including aducanumab, donanemab, lecanemab, and ALZ-801, have shown positive performance in patients with AD (Tolar et al., 2021). Despite reports of various side effects for aducanumab, it successfully passed the FDA approval process in 2021(Knopman and Perlmutter 2021). Nevertheless, donanemab ability to remove both cored and diffuse Aβ plaques has been evidenced by neuropathology reports in 2014 and showed an Aβ-reducing quality with fewer side effects than aducanumab. However, it has not yet received FDA approval.

Ramanan and Day (2023) administered lecanemab and donanemab every 2 and 4 weeks, respectively. They demonstrated that lecanemab caused lower Aβ-related imaging abnormalities (ARIA) rates and higher infusion reactions than donanemab (Ramanan and Day 2023). A randomized preclinical study on donanemab combination therapy with N3pG and β-site APP-cleaving enzyme (BACE) inhibitor (LY2811376) also showed 80% Aβ s removal from the brains of PDAPP-transgenic mice, while N3pG or LY2811376 treatment could clear about 50% of Aβ. Moreover, evaluation of the postmortem brain tissues of people with AD showed that donanemab could bond to about one-third of Aβ plaques, and highly reacted with the plaque core (Irizarry et al., 2016a; Lowe et al., 2021b). Therefore, donanemab was selected for comparison with the first medicine approved by the FDA, aducanumab, in this study. This review also attempts to summarize the latest data on aducanumab and donanemab as potential AD-modifying therapies to clar-

TABLE 1: Timeline of clinical trials of Aducanumab and key regulatory decisions

Author(s)	Year	Aducanumab approve Process
Liu et al	2011	The phase I clinical study of aducanumab trial began in the patients with mild to moderate AD.
Sevigny et al	2012	Phase Ib aducanumab trial was started in patients with mild AD.
Schneider	2015	Two phases III aducanumab trials, ENGAGE and EMERGE, started in MCI due to AD and mild AD dementia.
Schneider	2018	Prespecified futility analysis was conducted by Biogen based on data from the phase III trials.
Schneider	2019	- Studies ENGAGE and EMERGE were terminated by the Biogen. - Meeting with U.S FDA regarding termination were held.
Haeberlein et al	2020	After a filing by Biogen in early 2020, the U.S FDA stated the subsequent analyses did not provide adequate evidence for the efficacy of aducanumab.
Yang and Sun	2021	The U.S FDA approves aducanumab.

ify their advantages and disadvantages, and to develop viable therapeutic strategies for the future.

Medications and AD Treatment

Due to the numerous pathological aspects of AD, different agents are required for effective treatment (Sahni et al., 2011). The following four pharmacological classes were approved for patients with AD: 1) cholinesterase inhibitors (ChE-Is), such as rivastigmine, donepezil, and galantamine; 2) non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists (NMDA-RA); 3) dopamine agonists (D-A), namely memantine; and 4) Aβ-targeted agents, such as aducanumab (Sevigny et al., 2016).

Cholinergic System-targeting Drugs

The initial solution for decreasing the AD-induced symptoms was the administration of cholinergic precursors (Sahni et al., 2011), and acetylcholinesterase inhibitors (AchE-Is) were the first class of medications specifically approved by the FDA. On this point, tacrine, donepezil, rivastigmine, and galantamine were approved for AD treatment in 1993, 1996, 2000, and 2001, respectively (Aisen et al., 2012). Donepezil, as a selective AChE-I; galantamine as an allosteric nicotinic modulator and AChE-I; as well as rivastigmine, as a combined type of AchE and butyrylcholinesterase inhibitor (BChE-I) are used for treating mild-to-moderate AD; however, memantine is a candidate for moderate-to-severe AD symptoms (Aisen et al., 2012; Sahni et al., 2011).

AChE-Is bind to the AChE enzyme in the synaptic cleft, inhibit the enzyme, and prevent the early destruction of acetylcholine. Therefore, it remains longer in the cleft and increases the interactions between acetylcholine and cholinergic receptors (Aisen et al., 2012). The latest approaches have proposed the combination administration of various medicines. For instance, in patients with AD, the combination of ChE-Is and memantine was more effective than ChE-I alone (Touchon et al., 2014). Moreover, the combination of memantine with rivastigmine or donepezil produced beneficial effects in the treatment of mild-to-moderate or moderate-to-severe AD symptoms, respectively (Greig 2015). However, memantine has not been approved for the treatment of mild AD (Cummings et al., 2021b; Cummings et al., 2021a).

Aβ-targeting Medications

New recommended treatments for AD are active immunotherapy (vaccination) and passive immunotherapy with Aβ-targeting antibodies (Mo et al., 2017). Various pathological studies have also suggested that targeting Aβ was useful in patients with AD (Sevigny et al., 2016). Moreover, active anti-Aβ immunization was also effective in the prevention and treatment of the transgenic mice model of AD (Knopman et al., 2021). In addition, Aβ-targeting antibodies reduced Aβ accumulation in mice (Scearce-Levie et al., 2020). Consequently, several strategies, including the reduction of Aβ production, inhibition of Aβ aggregation, and enhancement of Aβ clearance, have been explored to decrease Aβ plaques

in AD (Table 1) (Frost and Zacharias 2020). Different medicines, such as anti-Aβ monoclonal and polyclonal (Igs) antibodies, Aβ aggregation inhibitors and antigens, γ-secretase inhibitors, and modulators, as well as BACE inhibitors, were not effective in mild-to-moderate patients with AD (Cummings et al., 2024; Knight et al., 2016; Panza et al., 2019; Paul et al., 2010). The reasons for the repeated failures in finding effective anti-Aβ agents for treating AD are unknown. Although the primary cause is unknown, the Aβ accumulation in the brain of AD patients could be the secondary failure agent (Panza et al., 2019). The Aβ plaques must be also reduced enough to show effective clinical improvement (Li et al., 2023). Late initiation of treatment, insufficient understanding of the pathophysiology of AD, and the dosage of medications are other reasons (Yiannopoulou et al., 2019).

Considering the fact that aducanumab has gained FDA drug approval and donanemab is in the final steps of this process, in this review, more attention will be paid to aducanumab and donanemab, as two new therapeutic strategies.

Aducanumab and Donanemab

Cummings et al. (2021) have reported that expert panel researchers have proposed six criteria for AD treatment with aducanumab in its early stage, including 1) a detailed history of cognitive symptoms, behavioral changes, and mental status; 2) confirmation of cognitive impairments by standard test; 3) neurological and physical examinations; 4) review of all medications currently used; 5) performing laboratory tests, such as complete blood cell count, electrolytes, hormones, and vitamins; and 6) magnetic resonance imaging to exclude other potential disorders (e.g., hydrocephalus, vascular dementia, and neoplasms) with similar symptoms (Cummings et al., 2021b).

Aducanumab has been developed by Neurimmune Therapeutics AG (a biotechnology company in Schlieren, Switzerland) and is marketed as 'Aduhelm' (Panza et al., 2016). Another pharmaceutical company (Biogen Inc., Massachusetts, United States), which produces aducanumab, terminated its clinical developments in March 2019 due to the observations, together with the outcome analyses in phase III trials, which did not show positive results for the reduction of cognitive impairment in patients with AD (Abyadeh et al., 2021; Costa and Cauda 2021).

To evaluate the efficacy and safety of aducanumab, Biogen Inc. conducted two studies on 3285 participants (aged 50-85 years from 20 countries) with early symptoms of AD (Tampi et al., 2021). Intravenous (IV) infusion of aducanumab was performed once every four weeks for an extended period of 76 weeks (Budd Haeberlein et al., 2022b). Subsequently, these participants were evaluated for positive brain Aβ pathology by positron emission tomography (Petch and Bressington ; Tampi et al., 2021). Aducanumab decreased the number of Aβ plaques in the phase 1b study (PRIME) and phase 3 trial (Sabbagh and Cummings 2021). Although aducanumab has already been authorized for the treatment of AD in the U.S. since 2003, Biogen declared its intention to apply for the U.S. FDA license in October 2019 as a treatment method for patients with AD (Petch and Bressington 2021). Finally, in June 2021, aducanumab received FDA approval for the treatment of AD through an accelerated approval mechanism (Knopman and Perlmutter 2021; Yang and Sun 2021). Notably, accelerated approval allows for a medication to be marketed prior to the completion of a randomized controlled trial (Glymour 2021). Therefore, aducanumab was claimed to be the first approved medicine to diminish the number of Aβ plaques (Cummings et al., 2021b). Moreover, it is considered the first treatment for mild cognitive impairment and the first medicine with a putative disease-modifying mechanism for treating AD (Sabbagh and Cummings 2021; Yang and Sun 2021). Before aducanumab, the main treatment goal for AD patients was to reduce cognitive impairment and behavioral disturbances by serotonin reuptake inhibitors (SSRIs), ChE-Is, NMDAR antagonists, and selective SSRIs or serotonin-noradrenaline reuptake inhibitors (Gunawardena et al., 2021).

Similar to aducanumab, donanemab (for example, N3pG-Aβ or LY3002813) is an IgG1 mAb that targets Aβ plaques and is developed from murine mE8-IgG2a (Mintun et al., 2021a). Donanemab is one of the newest monoclonal antibodies (mAbs), which removes Aβ plaques in AD patients through microglial-mediated phagocytosis (Decourt et al., 2021; Lowe et al., 2021a; Lowe et al., 2021b). In a study by Mintun et al. (2021), donanemab was more effective than a placebo in improving cognition in patients with AD (Mintun et al., 2021a). In the phase 1b study, donanemab reduced the

TABLE 2: Timeline of clinical trials of Donanemab and key regulatory decisions

Author(s)	Year	Donanemab Trials Process	References
Lilly Company	2013	Phase 1 of the Donanemab human study was conducted by Lilly Company from May 2013 to August 2016 on 100 patients with mild AD and memory impairment which had a PET-positive amyloid scan.	[44]
Lilly Company	2015	Lilly started a second Phase 1 (Phase 1b) study in 150 patients MCI due to AD or mild to moderate AD.	[44]
Lilly Company	2017	Lily began TRAILBLAZER-ALZ, in which the safety, tolerability, and efficacy of the combination of the two drugs Donanemab alone and in combination with the BACE inhibitor were evaluated.	[44]
Lilly Company	2020	To assess the safety and efficacy of TRAILBLAZER-ALZ 2 as phase 2, Lily initially recruited 500 patients with AD.	[44]
Lilly Company	2021 (August)	Lilly and the Banner Alzheimer's Institute began a Phase 3 prevention trial.	[44]
Lilly Company	2021 (November)	Lily started TRAILBLAZER-ALZ 4 as Phase 3 to compare the clearance rate of amyloid plaques by aducanumab and donanemab	[44]

number of Aβ plaques in patients with mild-to-moderate AD (Fleisher et al., 2018; Mintun et al., 2021a). In one study, the murine surrogate of donanemab reduced the number of plaques in the APP transgenic mice (Gunawardena et al., 2021).

Concerning the use of donanemab, Lilly and company conducted phases 2 and 3 clinical trials TRAILBLAZER-ALZ (NCT03367403) and TRAILBLAZER-ALZ 2 (NCT04437511), respectively, to assess the safety, tolerability, and efficacy of this agent for patients with early symptomatic AD. The TRAILBLAZER-ALZ trial selected 272 patients based on cognitive evaluations, Aβ plaque imaging, and tau framework through PET imaging (Rashad et al., 2022).

Although donanemab has not yet received FDA drug approval, it showed fewer side effects compared to aducanumab. Therefore, it is currently under investigation to be used for the treatment of primary AD (Mintun et al., 2021a). However, both aducanumab and donanemab had significant effects shown by tau PET imaging (Tolar et al., 2021).

Aducanumab and Donanemab Trials

Aducanumab has been evaluated in several trials (Table 2), including three trials at different doses, a phase 1b study (PRIME), and two phase 3 trials (EMERGE and ENGAGE). PRIME is an ongoing randomized, placebo-controlled, phase 1b study of the aducanumab antibody in patients with mild AD (Chiao et al., 2019). EMERGE and ENGAGE are also two identically designed phase 3 trials that evaluated the efficacy and safety of aducanumab in patients with early AD (Budd Haeberlein et al., 2022a). A total of 3285 patients (aged 50-85 years from 348 sites in 20 countries) with mild cognitive impairment (MCI) or mild AD participated in these trials (Budd Haeberlein et al., 2022b; Coerver et al., 2021; Synnott et al., 2021). The first clinical trials (phase 1) for aducanumab started in 2011 (Gunawardena et al., 2021) after preclinical studies in mice with AD, in which aducanumab had reduced the number of plaques (Gamage and Kumar 2017). In the PRIME study, administration of aducanumab at a dose of 10 mg/kg not only reduced the Aβ plaques dose- and time-dependently, but also improved the cognitive impairment. Subsequently, the EMERGE and ENGAGE trials were performed after the PRIME trial and were both stopped after confirming the futility and inefficiency of the analysis (Coerver et al., 2021). In these trials, patients received low-dose aducanumab, high-dose aducanumab, or placebo via IV infusions (Budd Haeberlein et al., 2022b). The ENGAGE trial showed no differences between the lower (3 mg) and higher (10 mg) doses of aducanumab compared to the placebo (Thomas et al., 2021). However, after receiving aducanumab at a dose of 10 mg/kg, an improvement in clinical disturbance was observed. Similar to the PRIME trial, both following studies showed a dose- and time-dependent reduction in Aβ plaques (Coerver et al., 2021).

Based on a study by Thomas et al. (2021), the EMERGE and ENGAGE trials were performed with the same design under double-blind, randomized, placebo-controlled conditions for 18 months. Due to inef-

fectiveness, the EMERGE trial was terminated early; however, subsequent analyses showed beneficial effects at higher doses (Thomas et al., 2021). Similarly, the ENGAGE trial did not show advantageous effects at higher doses. Liu et al. indicated that in the EMERGE trial, high-dose aducanumab was better than placebo (Tampi et al., 2021). Seven months after discontinuing the aducanumab clinical development, in December 2019, Biogen announced its efficacy (Costa and Cauda 2021). Although the drug approval procedure usually depends on achieving appropriate results from two clinical trials, aducanumab was approved based on two studies, both of which were discontinued due to the lack of proper results. In subsequent analyses of trial data, only one of the trials showed significant results from high-dose aducanumab therapy. An infusion of aducanumab was associated with brain edema and hemorrhage in more than a third of the patients. Therefore, the U.S. FDA formed an advisory committee of external experts to review the available data. This committee concluded that the evidence did not support the efficacy of aducanumab in reducing cognitive decline (Chiong et al., 2022). Finally, during 18 months of clinical trials, the U.S. FDA confirmed the inconsistency of clinical advantages concerning aducanumab. Moreover, some studies have shown that reducing Aβ in the brain via inhibiting β- or γ-secretase could not improve cognitive performance and led to worsened conditions. In addition, in the phase 3 trial, aducanumab-induced changes in cognitive performance were not associated with a decrease in Aβ in the brain (Knopman and Perlmutter 2021). To diagnose Aβ pathology, PET was used in clinical trials. Other types of tests, including the cerebrospinal fluid (CSF) analysis of Aβ, were also consistent with the PET scans (Coerver et al., 2021). Overall, the biomarkers showed pathophysiological changes in EMERGE and ENGAGE, but the clinical results did not show significant beneficial effects. Regarding the cause of this event, there is a need for further investigation in the process of studies or data analysis (Budd Haeberlein et al., 2022a; Knopman et al., 2021).

Lilly and company also conducted a Phase 1 human study on donanemab (May 2013-August 2016) on 100 patients with mild AD and memory impairments, having PET-positive Aβ scans. This study evaluated five different doses (0.1-10 mg/kg, monthly infusion) given a single subcutaneous injection against a placebo (Irizarry et al., 2016b; Lowe et al., 2021b; Mintun et al., 2021b).

In December 2015, due to positive pharmacodynamics findings from the phase 1a study, Lilly and company started the second phase 1 (phase 1b), a randomized and placebo-controlled study on 150 patients (Irizarry et al., 2016b; Lowe et al., 2021a). The general purpose of the phase 1b study was to evaluate the immunogenicity of the medicine at different doses and its ability to reduce Aβ plaques. This study aimed to understand the effect of donanemab on the brain Aβ plaque load using PET imaging and assess the safety, pharmacokinetics, immunogenicity, and cognitive function alterations following the IV doses of donanemab (Lowe et al., 2021a). In this trial, three different doses were administered. The first dose was a single dose of 10, 20, or 40 mg/kg, the second dose was 10 mg/kg given every other week for 24 weeks, and the third dose of 10 or 20 mg/kg was injected every month for 16 months. The main findings of this study indicated that the single dose (up to 40 mg) and multiple doses (up to 20 mg/kg) of donanemab reduced Aβ plaque deposits in patients with AD and the reduction of observed Aβ plaques by donanemab was rapid, robust, and sustained (Lowe et al., 2021a). Almost all patients treated with donanemab developed anti-drug antibodies and donanemab was well tolerated with ARIA-E. One-fourth of patients developed ARIA-E, mostly asymptomatic and another quarter of patients exhibited infusion reaction. After the termination of this trial in August 2019, reports of monthly doses of 10 or 20 mg/kg for 16 months demonstrated the reduction of Aβ (Lowe et al., 2021a).

In December 2017, Lilly and company began TRAILBLAZER-ALZ, in which the safety and efficacy of donanemab alone and in combination with BACE inhibitors were evaluated in 375 patients with memory impairment and positive PET scan. In October 2018, Lilly and company stopped this combination but continued to evaluate donanemab alone. In January 2021, they announced that the ongoing trial phase had met its primary endpoint and although not all results were statistically significant, donanemab had reduced the Integrated Alzheimer's Disease Rating Scale (iADRS) and improved cognitive functions (Wessels et al., 2015). According to the data, ARIA-E was developed in 27% of patients, with 6% of cases being symptomatic. In addition, at the end of the trial, some patients (66% approx.) were Aβ -negative. Donanemab slowed the accumulation of

tau proteins in the frontal cortex and other areas of the brain. In addition to ARIA-E, participants who received treatment had more ARIA-H, superficial siderosis (due to small brain bleeding), and nausea. The adverse effects and death risks were not different in groups, and anti-drug antibodies were developed in 90% of patients. Loss of brain volume is sometimes attributed to Aβ removal; however, its extent and timing, relative to donanemab administration, may indicate other causes, most possibly inflammation (Ayton 2021).

In October 2020, Lilly and company began the TRAILBLAZER-ALZ 2 process on 500 patients as a phase 2 safety and efficacy trial. Only patients with at least 6 months of memory loss, MMSE scores 20-28, as well as Aβ and tau PET scan criteria, were eligible to enter the trial. After 18 months of receiving donanemab or placebo, the primary outcome changed in terms of Clinical Dementia Rating (CDR) scale Sum of Boxes (CDR-SB); subsequently, MMSE, ADAS-Cog13, iADRS, ADCS-iADL, Aβ and tau PET scans, volumetric magnetic resonance imaging (MRI), pharmacokinetics, and measures of anti-donanemab antibodies were assessed. By early 2024, the continuation of these trials will be finished in different countries (Zimmer et al., 2022). The donanemab trials are summarized in Table 3. In June 2021, the US FDA granted a breakthrough therapy designation to accelerate its development. In October of the same year, by submitting the sequential trial data, Lilly and the company applied for a license under the same accelerated approval pathways that had already been used for aducanumab (Budd Haeberlein et al., 2022a).

Simultaneously, in August 2021, Lilly and Banner Alzheimer's Institute launched a phase 3 prevention trial, called TRAILBLAZER-ALZ 3 to evaluate 3,300 cognitively-normal participants (aged 50-55 years) at a high risk of AD based on their increased tau plasma levels. The clinical progression time measured by the CDR scale will be the primary outcome. Participants receive monthly injections of donanemab or placebo for 9 months and are monitored every 6 months until 343 people are assessed as cognitively impaired, defined as a high CDR zero score in two consecutive assessments. Cognitive tests also verify the concentration of donanemab and anti-donanemab antibodies in plasma Drug infusions, blood sampling, and MRI are performed in local centers; however, this test will be evaluated through video calls. The test will have been conducted by September 2027 in the United States (more than 80 sites) (Rashad et al., 2022).

Furthermore, in November 2021, Lilly and company began TRAILBLAZER-ALZ 4 as a comparison between the effect of donanemab and aducanumab concerning plaque clearance. Each month, 200 patients with positive Aβ PET scans were randomly assigned to either aducanumab treatment or IV donanemab. The primary objective was to obtain the number of patients with complete clearance of Aβ plaques as evaluated by florbetapir PET. The secondary outcome will be related to the Aβ PET measurements over 18 months. Notably, the experiment is expected to continue in more than 30 locations inside the United States until 2023 (Glymour 2021).

A double-blind, randomized, placebo-controlled, single-dose study by Lowe et al. on patients with MCI due to AD demonstrated the general safety and tolerability of donanemab (Decourt et al., 2021). Other studies did not show significant changes in plasma Aβ after donanemab administration at any doses. In addition, no significant change in cognitive status was observed (Lowe et al., 2021b).

A study by Mintun et al. (2021) on 257 patients with AD divided them into two groups who received donanemab or placebo. Tau levels and Aβ plaque deposition were confirmed in AD patients with PET scans before the experiment. The cognitive status of patients was evaluated with AD progression-specific tests and its improvement was observed as the primary outcome. However, no significant differences were observed in the secondary outcomes. Study results showed a reduction in Aβ plaques in the group receiving donanemab compared to placebo. Nevertheless, the results did not demonstrate any significant differences at the individual level (Mintun et al., 2021a).

Aducanumab and Donanemab Application Criteria

Patients with mild AD could take other medicines, consisting of ChE-Is, before or after treatment with aducanumab. There are presently no specified studies on the administration of aducanumab in moderate-to-severe AD (Cummings et al., 2021b). However, to assess the suitability of aducanumab, it is important to determine the Aβ burden in an AD patient before treatment by using a PET scan and CSF analysis (Gunawardena et al., 2021). The patient's eligibility consists of the subse-

TABLE 2: Aβ-targeting Drugs

Type	Name	Target	Disease Stage	Mechanism
Anti-Aβ monoclonal antibodies	Lecanemab (Leqembi)	Soluble and insoluble Aβ (oligomers, protofibrils, and insoluble fibrils)	Early AD or mild cognitive impairment	↓Aβ (neutralizing and eliminating)
	Aducanumab (Aduhelm)	Soluble and insoluble Aβ (the oligomeric and fibrillary states) Targets amyloid as it begins to form fibrils	Early AD or mild cognitive impairment	●↓ Aβ (binds to a linear epitope formed by Aβ amino acids 3 to 7) ●↑NMDA receptors permeability to calcium
	Donanemab	Targets an epitope at the N-terminal of a pyroglutamate Aβ (p3-42).	Early AD or mild cognitive impairment	Induction of Microglial-mediated clearance of existing Aβ plaques
Anti-Aβ polyclonal antibodies or immunoglobulins	Baxter IG	Soluble and insoluble Aβ aggregates	●Moderate stage of AD ●Carriers of APOE e4 alleles	●Production antibody-Aβ complexes ●Antibody inhibition of Aβ aggregation ●Peripheral sink mechanism
Aβ aggregation inhibitors	Tramiprosate (3-APS, ALZ-801)	Soluble Aβ aggregates	●Mild-to-moderate of AD ●Carriers of APOE e4 alleles	●Anti-inflammatory effects ●Stabilization of Aβ-42 monomers ●Cholinergic transmission improvement
	Scyllo-inositol (ELND005, AZD103)	Insoluble Aβ aggregates	Mild to moderate AD	●Stabilization non-fibrillary non-toxic form of Aβ40, Aβ42 and peptide plaques ●Amelioration of oligomer neuronal autophagy ●Cholinergic transmission improvement ●Inhibition of α-synuclein aggregation
	Metal-chelating compound PBT2	Modulation metal-Aβ interactions	●Early AD ●Mild cognitive impairment	●Inhibition phosphorylation of the α- and β-isoforms of glycogen synthase kinase 3 ●Inhibition metal–binding residues of Aβ peptide ●Inhibition peptide aggregation
Aβ antigens (Vaccines)	AN-1792	Insoluble Aβ aggregates	Mild to moderate AD	●↑Antibody responses (Th1 polarization of the T cell response) ●↑pro-inflammatory cytokines ●Modulation activity /abundance of a small subpopulation of Aβ plaques
	AD02	Peptide epitope (Aβ N-terminus mimotope)	Early AD	●↑anti-Aβ antibodies ●↓pro-inflammatory TH1 response
	CAD-106	N-terminus Aβ1–6) B cell epitope linked to the capsid of the Qβ bacteriophage	Mild AD	↑anti-Aβ antibodies without activating Aβ-reactive T cells.
γ-secretase inhibitors	●GSI-953 ●LY-450,139 ●BMS-708,163	Active site of presenilin	Mild-to-moderate AD	●Inhibition of the γ-secretase cleavage of APP and Notch ●↓Total Aβ production.
γ-secretase modulators	●Tarenflurbil ●Indomethacin ●Sulindac ●Sulfide	Insoluble Aβ	Mild AD	●↑ Aβ37 or Aβ38 ●↓ Aβ42 ●Not affect Notch cleavage

Type	Name	Target	Disease Stage	Mechanism
β-site APP-Cleaving Enzyme (BACE) inhibitors	●LY2811376 ●LY2886721 ●AZD3839 ●Verubecestat ●Atabecestat ●Lanabecestat	Inhibition cleaves APP in the first step in β-amyloid (Aβ) peptide production	Mild-to-moderate AD	●↓Aβ1-34 ●↑Aβ5-40

AFFITOPEs peptides specific to Aβ (AD02), Amyloid precursor protein (APP), Avagacestat (BMS-708,163), Begacestat (GSI-953), Pre-aggregated Aβ42 with QS-21 adjuvant (AN-1792), Semagacestat (LY-450,139), 5,7-dichloro-2[(dimethylamino)methyl]-8-hydroxyquinoline (PBT2). References; Irizarry et al., 2016a; Lowe et al., 2021b, Cummings et al., 2024; Knight et al., 2016; Panza et al., 2019; Paul et al., 2010, (Knopman and Perlmutter 2021, Vaz and Silvestre 2020, Panza et al., 2016, Abyadeh et al., 2021; Costa and Cauda 2021

quent criteria:

Mild Cognitive Impairment (MCI): Patients with AD-induced MCI are candidates for treatment with aducanumab (Coerver et al., 2021).

Aβ positivity: The presence of β-Aβ plaques is one of the inclusion criteria in clinical trials, in which a PET scan is used. Moreover, the CSF analyses of Aβ 42, t-tau/Aβ 42 ratio, and p-tau 181/Aβ 42 ratio have similar results (Coerver et al., 2021).

Magnetic Resonance Imaging: The MRI scans are required to determine the possible contraindications to taking aducanumab, including hemorrhage, presence of cerebral infarction, and diffuse white matter disease (Coerver et al., 2021).

Although donanemab trials have not yet been completed, this medication was useful in the treatment of patients with MCI and mild-to-moderate AD (Budd Haeberlein et al., 2022a).

Aducanumab and Donanemab Advantages

Reducing Aβ plaques

Aducanumab (as an immunoglobulin) activates microglia to clear Aβ plaques (Abyadeh et al., 2021; Sabbagh and Cummings 2021). Therefore, it improves the cognitive impairments of AD patients caused by these plaques. As a benefit of aducanumab and unlike AChE agents, which only improve AD symptoms, it directly modulates the cause of the disease (Abyadeh et al., 2021; Aisen et al., 2012; Sahni et al., 2011). Single and multiple doses of donanemab have demonstrated a rapid and robust reduction in Aβ plaques in the brain (Lowe et al., 2021a). In other studies, the decrease in Aβ plaques has been greater in the donanemab group compared to the placebo group (Mintun et al., 2021a).

High affinity: Aducanumab is a high-affinity mAb (Coerver et al., 2022).

Decreasing CSF tau levels: Studies have shown that aducanumab significantly decreases CSF tau levels, which is a neurodegeneration biomarker (Abyadeh et al., 2021).

-Improving cognition: There is evidence that aducanumab improves cognition (Leinenga et al., 2021). Conversely, in some trials that involve aducanumab treatment, no cognitive improvement was observed, and cognitive status even worsened (Hershey and Tarawneh 2021). Moreover, donanemab had no statistically significant effect on the cognitive status at any dose. Furthermore, a larger phase 2 clinical trial over 76 weeks showed a significant reduction compared to the placebo. Although the patients treated with donanemab had improved cognitive status compared to the placebo, the differences were not statistically significant (Hershey and Tarawneh 2021). The cause of the low effect of Aβ reduction in the brain on cognitive impairments is not precisely known. Some studies have suggested that reducing Aβ load in the brain alone is not enough and probably soluble Aβ monomers should also be reduced to reveal cognitive effects on Alzheimer's patients (Imbimbo et al., 2023).

-Restoring impaired calcium homeostasis: There is evidence that the aducanumab analog, Adu, has restored calcium homeostasis, which was impaired in the AD mouse model (Kastanenka et al., 2016).

-Acceptable toleration: Administration of donanemab up to 10 mg/kg has generally been well-tolerated. The mean terminal elimination half-life after a single-dose administration at 0.1-3.0 mg/kg doses was approximately 4 days and increased to almost 10 days at a dose of 10 mg/kg. In addition, the IV infusion of a 10 mg/kg dose of donanemab could reduce Aβ deposits in AD despite having a shorter-than-expected half-life (Lowe et al., 2021b).

Pharmacokinetics and Pharmacodynamics

Aducanumab (BIIB037) is a human IgG1 mAb that selectively binds to parenchymal Aβ in the brain (Abyadeh et al., 2021; Arndt et al., 2018; Sevigny et al., 2016; Thomas et al., 2021). Large-sized antibodies, such as aducanumab, would be broken down into oligopeptides and amino acids by lysosome after entering the cell through endocytosis or pinocytosis (Beshir et al., 2022; Ryman and Meibohm 2017).

In addition, aduhelm has been reported to reduce CSF phosphorylated tau (p-Tau) and total tau (t-Tau) levels, with higher levels found in the medial temporal, temporal, and frontal brain regions. In summary, the injection of higher doses of aduhelm was associated with a greater reduction of Aβ plaques in the brain. Pharmacokinetic results indicated that steady-state aduhelm concentrations can be achieved through a repeated dosing regimen of 16 weeks every four weeks. Systemic accumulation of aduhelm was reported 1.7-fold. The maximum concentration of aduhelm increased the dose proportionally in a dose of 1-10 mg/kg every four weeks, with a steady-state volume distribution of 9.63 L (Budd Haeberlein et al., 2022a).

Similar to endogenous IgGs, aduhelm may be broken down into small peptides and amino acids via catabolic pathways and in the same manner. Its clearance was 0.0159 L/h, and its terminal half-life was 24.8 days. Race, gender, body weight, and age affected exposure to aduhelm but not significantly (Budd Haeberlein et al., 2022a). Not only no urinary excretion was observed, but also biliary excretion was very low (Ryman and Meibohm 2017). The clearance and half-life of aducanumab have been reported as 0.0159 L/h and 24.8 days, respectively (Beshir et al., 2022).

Donanemab, originally known as 'LY3002813', is a human IgG1 mAb directed at an N-terminal pyroglutamate Aβ epitope. Donanemab removes Aβ plaques through microglial-mediated clearance (Lowe et al., 2021b). The mean half-life of donanemab after a 20 mg/kg single dose was less than 10 days (Lowe et al., 2021a).

The mean terminal elimination half-life with a single IV dose of 0.1-3.0 mg/kg also was 4 days, while was 10 days for a 10 mg/kg dose. In addition, only the 10 mg/kg dose showed alterations in Aβ PET (40%-50% reduction in Aβ). Moreover, the administration of a single IV dose led to the production of anti-drug antibodies in 90% of subjects after 3 months (Lowe et al., 2021b).

Plaque Clearance Mechanism

Aducanumab selectively targets Aβ aggregates, such as insoluble fibrils and soluble oligomers, by binding to the amino terminus of Aβ in the antibody (Leinenga et al., 2021; Thomas et al., 2021). Studies have shown a high aducanumab affinity for Aß plaques (Cummings et al., 2021c). By crossing the blood-brain barrier, aducanumab binds to Aβ plaques after entering the brain. The binding of aducanumab to these plaques eventually stimulates microglia to clear the Aβ plaques, reducing the burden of Aβs in the brain (Sabbagh and Cummings 2021). However, previous trials provided insufficient evidence regarding the improvement of cognitive test scores by the aducanumab-induced reduction of Aβ plaques (Retinasamy and Shaikh 2021).

Aducanumab was derived through a reverse translation process from the blood B-lymphocytes of healthy individuals (cognitively normal) or those with a slow cognitive decline whose immune systems had successfully resisted AD (Leinenga et al., 2021; Panza et al., 2016). It should be noted that lymphocyte antibody genes are used to generate recombinant human antibodies (Cummings et al., 2021b).

The study by Kastanenka et al. (2016) on the effect of aducanumab on plaque clearance showed that aducanumab may improve calcium regulatory dysregulation in AD (Kastanenka et al., 2016). In addition, the effect of aducanumab on calcium homeostasis in neurons was evaluated. Regulation of calcium homeostasis in neurons is essential, and disruption of calcium regulation leads to neuronal signaling impairments. Impairments of intracellular calcium in neurons cause some neurological diseases, such as AD. According to the available literature, it has not yet been proven whether the calcium hemostasis impairments are caused by the accumulation of Aβ plaques or the pre-accumulation of plaques. Nevertheless, there is evidence for the occurrence of calcium homeostasis impairment before the accumulation of Aβ plaques. Studies have also shown that neurons affected by the Aβ plaques increase calcium levels and protease activities. Calcium levels were increased by the Aβ plaques as they opened pores in cell membranes, thus, increasing the generation of reactive oxygen species. Moreover, aducanumab treatment has also reduced elevated calcium levels in a previous study

(Gamage and Kumar 2017).

Donanemab was recently introduced as a mAb targeted against specific epitopes on post-translationally modified Aβ plaques, which were only seen in the brains of AD patients (Aβ with pyroglutamate attached to the N-terminal). This modified form of Aβ remarkably tends to aggregate and deposit in the center of all Aβ plaques, however, only in the brain and is implicated in AD. The N-terminal truncation of Aβ and the subsequent enzymatic cyclization of the new end generate a specific incendiary Aβ. This two-step process leads to the production of a better drug target compared to the full-length version (Rostagno et al., 2022). After binding, donanemab causes microglial-mediated clearance of these plaques (Lowe et al., 2021b). Although it has been clear that donanemab removes Aβ plaques through microglial-mediated clearance, there is still no accurate or complete information on the clearance process.

Dosages

Aducanumab has shown immunity and tolerability in single doses (up to 30 mg/kg), and the maximum tolerated dose was 30 mg/kg (Ferrero et al., 2016). As measured by florbetapir-PET imaging, aducanumab treatment reduced the number of brain Aβ plaques during 12 months in a dose- and time-dependent manner (Panza et al., 2019; Sevigny et al., 2016). Studies in mice with AD showed a dose-dependent reduction in plaque size by this antibody (Gamage and Kumar 2017). Furthermore, monthly IV infusions of aducanumab over a year reduced the Aβ plaques dose- and time-dependently (Sun et al., 2018). Aducanumab was the first drug to show both Aβ reduction in the brain and positive effects on the cognitive state (Pais et al., 2020). Results indicated that after a three-week topical administration of aducanumab, a significant decrease and increase in Aβ plaque size and clearance were observed compared to the control group, respectively (Gamage and Kumar 2017). Unlike topical administration, the systemic administration of aducanumab did not diminish plaque size and clearance rate (Pritam Das 2001; Yona Levites 2006). According to Kastanenka et al. (2016)(46), the acute application of aducanumab resulted in the clearance of existing Aβ plaques in mice brains. In contrast, another piece of evidence in this study showed that chronic systemic administration of aducanumab for 6 months failed to reduce the number of Aβ plaques in 18- to 24-month-old mice. Consequently, aducanumab seems to be more effective for the prevention or treatment of amyloidosis at an early stage. However, it is not effective in the advanced stages. Moreover, treatment with aducanumab improved function without reducing the Aβ plaques in older mice (Kastanenka et al., 2016).

Before the FDA drug approval for aducanumab as an AD treatment, Cable et al. (2020) had indicated that even after its approval as an anti-Aβ drug, due to years of failed trials, it would still not be an ideal treatment for AD patients after the onset of symptoms (Cable et al., 2020). Finally, despite all ongoing controversies, aducanumab was adopted as the first anti-Aβ drug; however, several other types of drugs are under development (Vellas 2021).

Studies have reported that the administration of aducanumab (10 mg/kg) could reduce beta plaques in the brain with a half-life of fewer than 10 days (Lowe et al., 2021b). Moreover, according to the results from a phase 1a study on AD patients, donanemab with a similar 10 mg/kg dose decreased the number of Aβ plaques (Lowe et al., 2021a; Mintun et al., 2021a). Specific information on the dose and method of infusion for donanemab is not available, and only a dose-escalation study has been conducted. Therefore, although a dose of 10 mg/kg seems appropriate for reducing Aβ, more research is necessary to validate the accuracy of the appropriate dose.

Infusion

Aducanumab is administered as monthly IV infusions for an hour at different doses (the 1st and 2nd doses: 1 mg/kg; 3rd and 4th: 3 mg/kg; 5th and 6th: 6 mg/kg, and the 7th dose and subsequent doses: 10 mg/kg) (Cummings et al., 2021b). For the missing dosage, injection of the same dose has been suggested immediately after the recall (Budd Haeberlein et al., 2022a). Aducanumab is available in vials of 170 mg/1.7 mL or 300 mg/3 mL, which is added to 100 ml sodium chloride serum 0.9% for injection. According to previous studies, more than 6 months is required to reach the target dose of 10 mg/kg (Cummings et al., 2021b). In the phase 1b and phase 3 trials, the patients with early AD received IV infusions of aducanumab (10 mg/kg) with the same design, and dose-dependent plaque reduction was observed (Lin et al., 2022).

The appropriate time for the discontinuation of adu-

canumab administration has not been thoroughly studied. The appearance of the ARIA symptoms, patients' inability to adhere to the treatment, their decision, or the physician's recommendation might be the reasons to terminate the treatment process (Cummings et al., 2021b). For instance, MRI scans are recommended before the 7th and 12th infusions. If the radiographic examinations showed severe ARIA-hemorrhages (ARIA-H), while there was no increase in the number or size of ARIA-H on the MRI reports, the treatment program could be continued following the clinical evaluation (Budd Haeberlein et al., 2022a). Therefore, excessive caution is advised for ARIA during the initial eight doses of aduhelm administration (particularly for titration).

aducanumab treatment should be discontinued in all patients who show hypersensitivity reactions, such as urticaria and angioedema; in such cases, adequate treatment should be initiated. The effect of aducanumab in patients with moderate-to-severe AD has not been thoroughly studied (Cummings et al., 2021b; Budd Haeberlein et al., 2022a).

As donanemab has not been approved, specific information on the dose and method of infusion is not available. In a dose-escalation study, donanemab was administered at single, IV doses, including 0.1, 0.3, 1, 3, and 10 mg/kg, as well as 3 mg/kg SC. However, only IV injection at a dose of 10 mg/kg caused Aβ modifications (Lowe et al., 2021b).

Aducanumab and Donanemab Disadvantages

Aducanumab has some disadvantages, such as ARIA, anaphylaxis, stage-dependent AD treatment with aducanumab, and high price.

- ARIA: A significant risk of aducanumab infusion is a type of brain inflammation, known as ARIA, which includes a range of characteristics in the brain of AD patients diagnosed via MRIs (Salloway et al., 2022). Symptoms of brain inflammation include cerebral edema (ARIA-E), cerebral hemorrhage (ARIA-H), or their combination. More than 40% of patients who received aducanumab in the phase 3 trials experienced ARIA events (Chiong et al., 2022; Coerver et al., 2021).

Discontinuation of aducanumab infusion would be recommended for symptomatic, moderate, or severe ARIA (Cummings et al., 2021b). ARIA, the most common side effect of aducanumab, occurred in 35.2% of patients who received its high doses. The risk of ARIA, especially ARIA-E, was more common in patients carrying ApoE-4. Most ARIA events have occurred in the first eight doses of aducanumab infusions (Chiong et al., 2022; Coerver et al., 2021). In particular, ARIA was not always symptomatic and was mostly diagnosed by MRI in asymptomatic patients. Among aducanumab-receiving patients with ARIA symptoms, 67% had mild, 28% moderate, and 4% severe symptoms. The most common ARIA symptoms in the trials were confusion (5%), dizziness (4%), visual disturbance (2%), and nausea (2%). The ARIA symptoms are usually improved after 4-16 weeks; however, in patients with severe symptomatic ARIA, the aducanumab infusion should be discontinued (Cummings et al., 2021b). ARIA can appear as brain edema or sulcal effusion (ARIA-E) or as hemosiderin deposits caused by hemorrhage in the brain (ARIA-H). According to the radiographic examinations of the clinical trials, ARIA-E resolved after a few weeks and ARIA-H persisted for several weeks. The ARIA mechanism has not yet been elucidated; however, this mechanism could be a combination of increased cerebrovascular permeability (due to elevated clearance of Aβ plaques) or the direct effect of antibodies on the arteries that have led to the weakening of the vascular walls (Salloway et al., 2022). In the treatment of patients who received high doses of aducanumab in the EMERGE and ENGAGE studies, 41% of patients experienced ARIA, which was higher than the 10.3% of subjects in the placebo group (Gunawardena et al., 2021). Neurologists should consider both the benefits and risks of prescribing medications (Knopman and Perlmutter 2021). For instance, patients with an excess of cortical microbleeds and those receiving most anticoagulants should not receive aducanumab (Cummings et al., 2021b). In trials, 1 out of 10 patients who were receiving aducanumab, had symptoms, including headache, dizziness, confusion, visual disturbances, nausea, and vomiting. In rare cases, other symptoms, such as seizures, altered consciousness, neurological deficits, and high blood pressure were also observed (Chiong et al., 2022; Coerver et al., 2021).

Although ARIA-E was the most common side effect in the donanemab group compared to the placebo group, it was well-tolerated and completely resolved after the discontinuation of this medicine (Lowe et al., 2021a; Mintun et al., 2021a). In another study, no case of ARIA-E was observed, while ARIA-H was observed in several cases (Budd Haeberlein et al., 2022a). Al-

though two cases of ARIA micro-hemorrhage occurred in a previous study, no dose-dependency was observed in terms of incidence and severity. It should be noted that ARIA-E was not observed either. This is in contrast to other Aβ therapies, associated with treatment-emergent ARIA-E, as ARIA-E has been observed as early as a month after dosing (Lowe et al., 2021b). ARIA-E occurred in 12 of 46 patients treated with donanemab, 2 of whom were symptomatic with milder symptoms, such as headache, dizziness, drowsiness, and nausea. In addition, cerebral hemorrhage was observed in 6 out of 46 cases, whose ARIA-E was mostly drug-induced (Lowe et al., 2021a).

- **Anaphylaxis:** The IV infusion of aducanumab, similar to many other medications, carries a small risk of anaphylaxis (Thomas et al., 2021). Among 7.6% of the participants who received donanemab, infusion-related reactions were reported (Mintun et al., 2021a). In a study, 6 out of 37 patients had infusion reactions, including chills, flushing, dizziness, rash, fever, and anti-drug antibodies in their plasma (Budd Haeberlein et al., 2022a). The most common treatment-emergent adverse event of donanemab was a mild-to-moderate infusion-related reaction (Gunawardena et al., 2021).

- Bleeding: Some reports have suggested that, unlike some anti-plaque agents, donanemab did not cause bleeding (Budd Haeberlein et al., 2022a).

- **Effect of AD stage on treatment:** In a study by Kastanenka et al. (2016), the acute administration of aducanumab reduced Aβ plaques in mice. In this study, another evidence showed that chronic systemic administration of aducanumab for 6 months failed to reduce Aβ plaques in mice aged 18-24 months (Kastanenka et al., 2016).

- **Insufficient research:** Previous trials have not provided enough evidence for the effects of aducanumab in AD treatment among black, Asian, Latino, or other populations, as no specific study has been performed yet. Therefore, the administration of this medicine may have unexpected side effects in different groups (Glymour 2021).

- **High cost:** Another source of broad concern is the annual cost of $ 56,000 in the U.S. per patient, which might be difficult for the patients to cover. Surprisingly, this price is only related to the drug and there will be additional expenses for infusion services, physician follow-ups, and monitoring the risk related to the medicine infusion (Chiong et al., 2022; Gunawardena et al., 2021). Similar to aducanumab, donanemab has a very high cost as well (Eric L. Ross; Marc S. Weinberg; Steven E. Arnold 2022).

- **Monthly intravenous infusions:** Another disadvantage of aducanumab is the monthly IV injection and the need for drug injection services (Cummings et al., 2021b).

Summary and Conclusion

Key Findings and Insights from the Review

Aducanumab is the first medication developed to target Aβ plaques in AD, and the first one that has received U.S. FDA drug approval. Not only the role of Aβ plaques in AD is controversial, but also the results of existing studies are contradictory. Therefore, it is clear why there is still much debate over the effects of aducanumab on improving AD-related conditions. Recent research has shown that aducanumab could reduce the symptoms of AD, especially in the early stages of the disease; consequently, it could be an effective treatment for AD. On the other hand, it could cause ARIA (associated with edema and cerebral hemorrhage) and side effects, such as dizziness, nausea, vomiting, headache, seizures, altered consciousness, and high blood pressure. Aducanumab is currently very expensive. As a result, patients, governments, and insurance companies encounter a great challenge in obtaining this medication. Although it has been approved by the U.S. FDA, extensive and comprehensive research is still required to ensure its beneficial effects. On the other hand, donanemab, which seems to have fewer side effects compared to aducanumab, has not yet been approved by the FDA. It seems that the side effects of donanemab are fewer than aducanumab. According to previous studies, the effects of donanemab on the recognition and improvement of functions in AD patients have been contradictory.

Implications for Future Research and Clinical Practice

Due to the approval of aducanumab by the FDA, and Lilly's attempts for the approval application of donanemab to the FDA, it is necessary to develop clinical protocols and guidelines for the suitable administration and use of Aβ-targeting new medications. The FDA restricted aducanumab for MCI and mild AD patients, while many unclear and important subjects remain. First, need to pay more attention to the required safety monitoring

for Aβ serum biomarkers, CSF biomarkers, Aβ PET scans, and clinical efficacy outcomes. Second, the duration of treatment, cut-offs for the treatment schedule, and the CDR or MMSE required scores for a decision to continue or terminate treatment. Therefore, future pre-clinical or clinical trials need to further explain the mentioned doubts about aducanumab and donanemab.

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