

## REVIEW ARTICLE

# Implementation of monoclonal antibody therapy and new rehabilitation strategies for Alzheimer disease

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## Abstract

In June 2021, the United States Food and Drug Administration granted accelerated approval for aducanumab, the first monoclonal antibody drug to be used in clinical settings in the United States. Meanwhile, it has not received approval in Europe or in Japan owing to significant reduction of amyloid beta without evidence of slowing down the progression of cognitive decline of patients with early Alzheimer disease. In January 2023, routine approval was granted in the United States for a second antibody, lecanemab, which had sufficient evidence of clinical effect and significant deprivation of amyloid beta in the phase 3 trials. Lecanemab was approved by the Japanese regulatory authorities in Japan in September 2023 after Eisai filed for approval in January. A framework for treatment of Alzheimer disease with antibody therapeutics is required. Although lecanemab has demonstrated efficacy, side effects including amyloid-related imaging abnormality have also been confirmed. Based on the results of clinical trials, there is ongoing discussion of the system for its use in clinical settings. Lecanemab is expected to have disease-modifying effects and may inhibit the rate of cognitive decline in the early stage of Alzheimer disease, thereby prolonging the duration of mild stage period. This is also the period when the rehabilitation is most effective, making psychosocial interventions more important than ever. Rehabilitation techniques need to be developed for patients with early Alzheimer disease receiving disease-modifying therapy. Although disease-modifying drugs inhibit the progression of symptoms in the early stages for a certain period of time, once the threshold is exceeded, cognitive function may decline more rapidly than in non-drug-treated individuals. From this perspective, the effects of disease-modifying therapy are analogous to the effect of high cognitive reserve. These considerations should be taken into account to enhance the clinical utility of rehabilitation for patients under disease-modifying therapy for Alzheimer disease.

**Key words:** Alzheimer disease, immunotherapy, disease-modifying therapy, aducanumab, lecanemab, donanemab, rehabilitation

## INTRODUCTION

Alzheimer disease is a hot topic in the 21st century considering its high prevalence, severe disability and the long duration of the disease. However, the development of drugs for Alzheimer disease over the past 20 years has not always been smooth; dozens of candidate drugs have achieved good results in animal studies but the results could not be replicated in clinical trials.

Aducanumab, a monoclonal antibody targeting the amyloid  $\beta$ -protein, was granted accelerated approval in June 2021 by the United States Food and Drug Administration (FDA) with a conditional launch in the United States under the trademark Aduhelm™. Ac-

celerated approval is given for drugs for serious diseases based on improvement in surrogate endpoints that can be predicted to show clinical benefit. The FDA thus approved the use of aducanumab under the expedited approval framework with the condition that by February 2030 there must be verification of the real clinical benefit.

The development status of monoclonal antibody therapeutics (lecanemab, solanezumab, crenezumab, donanemab, and gantenerumab) have been previously discussed (Takeda, 2021). Following expedited approval of aducanumab in the United States, the manufacturers, Biogen and Eisai, filed for its approval with relevant regulatory authorities, but it was denied

Unlike symptomatic drugs, such as acetylcholinesterase inhibitors and N-Methyl-D-aspartate (NMDA) receptor antagonists, antibody therapeutics for Alzheimer disease have the potential to be disease-modifying therapy (DMT). The clinical use of Alzheimer DMT is totally different from that of symptomatic drugs, and there are many outstanding issues to be discussed.

## BACKGROUND OF DRUG DEVELOPMENT FOR ALZHEIMER DISEASE

One reason why the development of Alzheimer disease drugs is so difficult is because the pathology of Alzheimer disease is closely related to the brain's aging process. Forgetfulness in elderly people can be considered a physiological aging phenomenon of the brain. Worldwide, but especially in Japan, the av-



The inner ring shows Phase 3 agents; the middle ring comprises Phase 2 agents; the outer ring presents Phase 1 therapies; agents in green areas are biologics; agents in purple are disease-modifying small molecules; agents in orange areas are symptomatic agents addressing cognitive enhancement or behavioral and neuropsychiatric symptoms; the shape of the icon shows the population of the trial; the icon color shows the CADRO-based class of the agent ("Other" category includes CADRO classes that have three or fewer agents in trials). CADRO, Common Alzheimer's Disease Research Ontology; Tx, treatment (adopted from Cummings J, Zhou T, et al. Alzheimer's disease drug development pipeline 2023. *Alzheimer Dement* 9, e12385. 2023).

erage life expectancy has increased and many people are living longer, which suggests there will be an increasingly larger number of elderly people that will have brain-aging-related difficulties in daily life, and that dementia will become a widening social problem.

Alzheimer disease is currently understood to be a neurodegenerative disease characterized by cognitive decline with three hallmarks: senile plaques, neurofibrillary tangles, and neuronal degeneration in the cerebral cortex, as defined by CDC. Nonetheless, senile plaques and neurofibrillary tangles appear as the brain ages, and even in the brains of elderly people without cognitive decline. This suggests there is an overlap between Alzheimer disease and the physiological aging process of the brain.

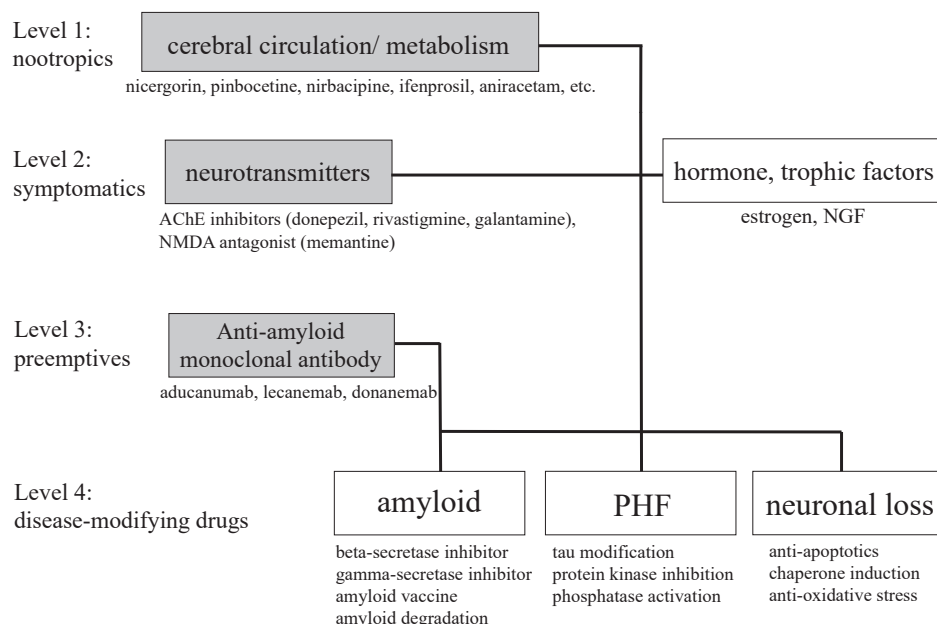
Molecular biochemical study of Alzheimer disease progressed in the 1980s to characterize senile plaques, neurofibrillary tangles, and neuronal loss. The amino acid sequence of amyloid deposited in senile plaques was determined, and the amyloid precursor protein gene was identified on chromosome 21. Hyperphosphorylated tau protein was identified as a component protein of neurofibrillary tangles, and subsequent research on Alzheimer disease has fo-

cused on the pathology of amyloid and tau.

Endeavors in Alzheimer drug development have continued for more than two decades without significant achievement, so it remains a hot area of research for many researchers and pharmaceutical companies worldwide. As of January 2023, there were 141 agents in 187 clinical trials for Alzheimer disease. In the pipeline are 36 agents in 55 trials in Phase 3, 87 agents in 99 trials in Phase 2, and 31 agents in 33 trials in Phase 1. Disease-modifying therapies represent 79% of the total number of agents in the trials, and 28% of candidate therapies are repurposed agents (Figure 1).

## HISTORY OF DRUG DEVELOPMENT FOR ALZHEIMER DISEASE

Pharmacotherapy for neuropsychiatric disorders began in the 1950s, with the development of drugs targeting each disorder, including antidepressants, antipsychotics, anxiolytics, sleep inducers, and antiepileptics. Cognitive impairment was also considered as a target of pharmacotherapy, and there was high expectations for the development of so-called nootropics (Figure 2, level 1). In the 1980s, 15 drugs



**Figure 2. History of Alzheimer disease drug development**

Red letters indicate drugs that have been introduced into clinical practice for the treatment of Alzheimer disease, and black letters indicate drugs that are not yet available in clinical practice. Many cerebral metabolic enhancers and cerebral circulation improving drugs were withdrawn after calcium hopantenate failed in reevaluation. Acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists were then widely used in clinical practice. For the next 20 years, attempts to develop drugs for Alzheimer disease were a series of failures. The framework of clinical trials was drastically changed, and the goal was shifted from clinical evaluation aimed at symptom improvement to prevention of clinical symptoms in subjects before the onset of the disease, with the aim of developing a preemptive drug. Based on these findings, aducanumab and lecanemab were approved as preemptive drugs, expected to have potential as disease-modifying therapy (DMT), but further validation is needed.

to improve cerebral circulation and eight cerebral metabolic enhancers were put on to the market, and clinicians at that time were very interested in the use of these drugs for patients with dementia. Cerebral metabolism enhancers were mainly used for Alzheimer disease and cerebral circulation improvers for vascular dementia (Table 1). Most of these were developed using calcium pantothenate as the control standard drug. However, calcium pantothenate failed to show sufficient clinical efficacy in a reevaluation, so in 1999, the Japanese Ministry of Health and Welfare requested a reevaluation of cerebral metabolic enhancers and drugs to improve cerebral circulation. As a result, only five components remained in the list of cerebral metabolism enhancers and brain circulation improvers: nicergoline (Sermion), nilvadipine (Nivadil), ibudilast (Ketas), vinpocetine (Karan), ifenprodil (Sorcoseril), and aniracetam (Draganon).

Around this time, the ‘acetylcholine hypothesis of Alzheimer disease’ was proposed, which explained the symptoms of Alzheimer disease as a decrease in acetylcholine in the basal forebrain nucleus and other areas. Attempts were made to develop drugs that would activate the acetylcholine system, including choline supplementation, acetylcholine synthase activators, muscarinic receptor agonists, and nicotinic

receptor agonists, but none were successful. Drugs that inhibit acetylcholinesterase, an acetylcholine-degrading enzyme in the brain, were then developed for the treatment of Alzheimer disease. Tacrine, the first of these drugs, is no longer used due to its hepatotoxicity, but others, such as donepezil, rivastigmine and galantamine, are still widely used in Japan. An NMDA receptor antagonist was subsequently developed later in Japan. All of these drugs are symptomatic treatment for Alzheimer disease, as cognitive decline in patients cannot be suppressed, despite their continued administration (Figure 2, level 2). The years of respective launch and characteristics of donepezil, rivastigmine, galantamine, and memantine in the United States, Europe, and Japan are listed in Table 2.

Despite researchers around the world working on this project as a top priority, the result has been a series of failures over 20 years. Candidate drug compounds were selected as lead compounds based on animal studies that had demonstrated efficacy in improving cognitive function of the experimental animals. When those compounds were tested in clinical trials, no compounds could successfully demonstrate the clinical efficacy for human use, and more than 20 compounds were dropped out or suspended the

**Table 1. Cerebral circulation improving drugs and cerebral metabolic enhancers marketed in Japan in 1980s and 1990s.**

In 1980s and 1990s many cerebral circulation improving drugs (A) and cerebral metabolic enhancers (B) were prescribed for dementia patients in Japan. After the failure of calcium hopantenate in reevaluation, most of these cerebral circulation improving drugs and cerebral metabolic enhancers were not used because they were evaluated in their clinical usefulness as calcium hopantenate as reference (adopted from Otomo, 1987).

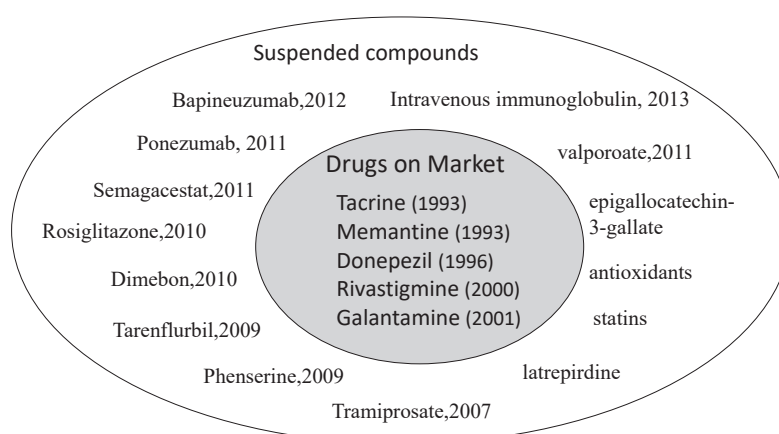
(A) Cerebral circulation improving drugs		(B) Cerebral metabolic enhancers	
Compound name	Trade Name	Compound name	Trade Name
Bencyclane	Halidor	ATP	Adephos
Brovincamine	Subromine	Ca hopantenate	Hopate
Cinnarizine	Aplactan	CDP-Choline	Nicolin
Cinepazide	Brendiel	Dihydroergotoxine mesylate	Hidergine
Cyclandelate	Capilan	r-aminobutyric acid	GammaronI
Dilazep	Comerian	Idebenone	Avan
Flunarizine	Furnal	Pyridoxine	Embol
Ifenprodil	Cerocral	Meclofenoxate	Lucidoril
Tocopherol	Ubera nicotinate		
Kallidinogenase	Kalicrain		
Moxisylyte	Moxiseal		
Nicardipine	Persipine		
Pentoxifylline	Torental		
Trapidil	Loconal		
Vinpocetine	Kalan		

development for clinical use. There are only five compounds approved for clinical use (Figure 3). There was thorough discussion of the reasons for the gap between preclinical and clinical trials, whether the amyloid cascade hypothesis itself is correct, and whether reducing amyloid alone is sufficient to achieve clinical efficacy. There has been growing consensus among researchers that it may be necessary to reconsider the nature of clinical trials for development of disease-modifying therapy for Alzheimer disease (Figure 2, level 4). The method of clinical trials was changed; originally it was one in which a candidate drug was administered in an effort to show significant differences in cognitive function, daily life function, and clinical

symptoms compared with a placebo. In the new method of clinical trials, the effectiveness of the drug is determined by examination of its ability to inhibit disease progression, rather than by improvement of symptoms. In other words, a new framework was proposed in which individuals with a high probability of developing Alzheimer disease would be included in clinical trials using biomarkers to evaluate whether or not the onset of the disease could be delayed. Clinical trials of drugs for Alzheimer disease under the new framework require a large number of participants (usually more than one thousand) and a minimum of 18 months to determine efficacy, so they require an enormous amount of time and effort.

**Table 2. Characteristics of Alzheimer disease drugs used in Japan**

	Developed year					
	USA	Europe	Japan	Registered name in Japan	Company	Dose
Acetylcholine esterase inhibitor						
Donepezil	1996	1997	1999	Aricept, Aricept D, Aricept granule 3 mg, 5 mg, 10 mg	Eisai	Start with 3 mg once/day, then increase to 5mg in 1-2 weeks. Can be increase to 10 mg in severe Alzheimer's disease
Rivastigmine	2000	2000	2003	Excelone patch 4.5 mg, 9 mg, 13.5 mg, 18 mg	Novartis	Start with 4.5 mg once a day, increase to 9 mg, 13.5 mg, and to 18 mg every four weeks
				Revastouch patch 4.5 mg, 9 mg, 13.5 mg, 18 mg	Ono Pharma	Start with 4.5 mg once a day, increase to 9mg, 13.5 mg, and to 18 mg every four weeks
Galantamine	2001	2000	2009	Reminyl, Reminyl OD (4 mg, 8 mg, 12 mg) solution (4 mg/mL)	Janssen Pharma	Start with 4 mg tablet twice a day, then increase to 8 mg twice a day. Can be increased to 12 mg twice a day for some cases.
NMDA antagonist						
Memantine	2003	1993	2011	Memantine, memantine OD 5 mg, 10 mg, 20 mg	Daiichi-Sankyo	Start with 5 mg per day, then increase by 5mg in every week, up to 20 mg



**Figure 3. Drugs developed and marketed between 1996 and 2020, and drugs dropped out during development**

Tacrine was launched globally in 1993 as the first Alzheimer disease drug with acetylcholinesterase inhibition, but it was not widely used due to liver toxicity. Memantine, an NMDA antagonist, was launched in Europe in 1993, the figure shows the year in which it was first introduced across the world. In addition to these successful Alzheimer disease drugs, dozens of other compounds have been developed for the treatment of Alzheimer disease, but none of them had been successful until 2020.

## Aducanumab

Aducanumab is the first amyloid- $\beta$  targeted monoclonal antibody that has been shown to reliably reduce plaques in the brain by positron emission tomography (PET) in a dose-dependent manner (Sevigny, 2016). In 2021, the FDA granted expedited approval of aducanumab for the treatment of mild cognitive impairment (MCI) or mild dementia due to Alzheimer disease based on the biomarker signal of amyloid- $\beta$  reduction in the brain. Conflicting evidence of clinical efficacy in two phase 3 trials of aducanumab, which were terminated early based on pooled futility analyses, has led to controversy over unclear evidence of the drug's clinical efficacy, the risk of serious side effects, and concerning the study population. The decision for approval was controversial due in part to the lack of patient diversity, the high cost of the drug, and an opaque approval process that was 'riddled with fraud' according to one congressional investigation (Alexander, 2021; Budd, 2022; Rambinovic, 2021). Insurers in the United States, including the Centers for Medicare and Medicaid Services, have severely restricted insurance coverage, limiting any moves to develop the substantial infrastructure needed for appropriate and safe administration, so the reality is that aducanumab is rarely used in the United States. Aducanumab is being considered for approval by the European and Japanese regulatory offices, but it has not yet been approved for clinical use.

## Lecanemab

Amyloid- $\beta$  (A $\beta$ ) is present in the brain as soluble aggregates such as monomers, small dimers and trimers, large oligomers and protofibrils (PF), as well as insoluble fibrous amyloid fibrils deposited in the core of senile plaques and in the vessel walls. Lecanemab is a humanized IgG1 monoclonal antibody that selectively binds to soluble protofibrils and removes it via phagocytosis by microglia, thereby preventing the deterioration of clinical condition caused by progression of Alzheimer disease.

In January 2023, lecanemab became the second A $\beta$ -targeted monoclonal antibody after aducanumab to receive FDA approval (Swanson, 2021). In the phase 3 CLARITY AD trial, patients with MCI or mild Alzheimer disease who received lecanemab showed a 27% slower decline compared with a placebo on the primary endpoint of change in Clinical Dementia Rating-Sum of Boxes (CDR-SB) (Van Dyck, 2023). Based on this clinical efficacy evidence, the FDA granted lecanemab routine approval in July 2023.

The phase 3 CLARITY AD study of lecanemab was

a multicenter, double-blind, phase 3 trial in patients aged 50-90 years with early Alzheimer disease (MCI or mild dementia due to Alzheimer disease) with evidence of amyloid deposition on PET or cerebrospinal fluid testing. Participants were randomized in a 1:1 ratio to receive intravenous lecanemab (10 mg per kg of body weight every 2 weeks) or placebo. The primary endpoint was change from baseline in CDR-SB score at 18 months, and secondary endpoints were change in amyloid burden according to PET, the Alzheimer Disease Assessment Scale (ADAScog14; range 0-90; the higher the score, the greater the impairment), the 14-item cognitive subscale of the Alzheimer Disease Assessment Scale (ADCOMS; range 0-1.97; the higher the score, the greater impairment), and the Activities of Daily Living Scale for Mild Alzheimer Disease ADCS-MCI-ADL (range: 0-53; the lower the score, the greater impairment).

A total of 1795 participants were enrolled, with 898 assigned to lecanemab and 897 to a placebo. The mean CDR-SB score at baseline was approximately 3.2 in both groups; the adjusted least squares mean change from baseline at 18 months was 1.21 in the lecanemab group and 1.66 in the placebo group (difference -0.45; 95% confidence interval [CI] -0.67 to -0.23;  $p < 0.001$ ). There was a greater reduction in cerebral amyloid burden in the lecanemab group than in the placebo group (difference -59.1 centiloids; 95% CI, -62.6 to -55.6). Other two-arm mean differences favoring the lecanemab-treated group in change from baseline were as follows: -1.44 (95% CI, -2.27 to -0.61;  $p < 0.001$ ) for the ADAS-cog14 score, -0.050 (95% CI, -0.074 to -0.027;  $p < 0.001$ ); and 2.0 (95% CI, 1.2 to 2.8;  $p < 0.001$ ) for the ADCS-MCI-ADL score. Lecanemab treatment resulted in injection-related reactions in 26.4% of participants and amyloid-related imaging abnormalities (ARIA) with edema or effusion in 12.6% of participants.

In summary, lecanemab reduced markers of amyloid in early Alzheimer disease, resulting in a moderate degree of cognitive and functional decline at 18 months compared with a placebo. However, it was associated with adverse events, so longer trials are needed to clarify the efficacy and safety of lecanemab in early Alzheimer disease.

Based on data from the aforementioned phase 3 Clarity AD clinical validation study, an application was approved by FDA on January 7, 2023. Subsequently, a marketing authorization application was submitted in Europe on January 11, 2023 and in Japan on January 16, 2023. After an agreement for approval was reached through deliberations at committee meetings

in July and August 2023, lecanemab (Leqembi) has been approved for clinical use in Japan on September 25, 2023. Leqembi 200mg and 500mg for intravenous infusion will be marketed by the end of 2023, after the drug price is determined for coverage by national health insurance of Japan.

### Donanemab

Donanemab is an immunoglobulin G1 monoclonal antibody that binds to N-terminal truncated insoluble beta-amyloid to remove the plaques through microglia-mediated phagocytosis. TRAILBLAZER-ALZ2, a phase 3 clinical trial, was a randomized, double-blind, placebo-controlled, 18-month dosing of donanemab in patients from 277 sites (eight countries) with PET-positive, symptomatic early Alzheimer disease (MCI and mild Alzheimer disease) (Sims, 2023). Subjects were randomized approximately 1:1 to donanemab ( $n = 860$ ) or to a placebo ( $n = 876$ ) administered by intravenous infusion every 4 weeks for 72 weeks. The primary endpoint was change in iADRS scores from baseline to week 76 (range 0-144, with lower scores indicating greater disability). There were 24 assessment items, including primary, secondary, and descriptive items, and one of the secondary assessment items was the change in CDR-SB scores (range 0-18, with higher scores indicating greater disability). The 1736 randomly assigned subjects had a mean age of 73.0 years, 996 were female (57.4%), 1182 had low/moderate tau pathology (68.1%), and 552 had high tau pathology (31.8%). Of these subjects, 1320 completed the trial (76%), with significant differences in 23 of the 24 items.

The change in iADRS scores at week 76 for the low/moderate tau pathology group was -6.02 (95%CI, -7.01~-5.03) in the donanemab group and -9.27 (95%CI, -10.23~-8.31) in the placebo group, a significant difference of 3.25 points [95%CI, 1.88~-4.62] ( $p < .001$ ). Overall, the difference was -10.2 (95%CI, -11.22~-9.16) in the donanemab group versus -13.1 (95%CI, -14.10~-12.13) in the placebo group ( $p < .001$ ). The change in CDR-SB scores at week 76 was also significantly higher for the low/moderate tau pathology group: 1.20 (95%CI, 1.00-1.41) in the donanemab group and 1.88 (95%CI, 1.68-2.08) in the placebo group, a significant difference of -0.67 [95%CI, -0.95~-0.40] ( $p < .001$ ). The overall comparison was 1.72 (95%CI, 1.53-1.91) in the donanemab group and 2.42 (95%CI, 2.24-2.60) in the placebo group, a significant difference of -0.7 [95%CI, -0.95~-0.45] ( $p < .001$ ). The edematous form of ARIA as a side effect occurred in 205 patients in the donanemab

group (24.0%; 52 of them had symptoms) and in 18 patients in the placebo group (2.1%; no patients had symptoms). Adverse reactions during infusion occurred in 74 patients (8.7%) in the donanemab group and four patients (0.5%) in the placebo group. There were three deaths during the trial in the donanemab group and one death in the placebo group.

In this study, donanemab delayed iADRS scores predominantly in the group with less tau pathology and in patients overall. The donanemab group was clinically significant ( $> 20\%$  delay in clinical deterioration) in iADRS and CDR-SB. This was true for both the low tau pathology group and the overall group. There was a reduced risk of progression on the CDR-G in 38.6%. Over 18 months, progression was delayed by 4.4-7.5 months. In addition, 47% of the donanemab group showed no change in CDR-SB at 1 year.

Eli-Lilly applied for the approval of donanemab to Japanese authorities in September 2023. Considering the sufficient data from the phase 3 clinical trial of donanemab, it is expected donanemab will be approved as the second monoclonal antibody therapy for Alzheimer disease in Japan by 2024.

### Challenges with the launch of disease-modifying therapy for Alzheimer disease

Antibody therapeutics for Alzheimer disease with recently reported success are based on the amyloid cascade hypothesis and are drugs that attempt to suppress the pathogenesis of Alzheimer disease by reducing the amount of amyloid deposition by removing amyloid beta, which is cut out and produced from the amyloid precursor in the brain. At a time when strategies to inhibit the production and aggregation of amyloid- $\beta$  in the brain were thought to be effective,  $\gamma$ -secretase inhibitors and  $\gamma$ -secretase modulators were developed based on the idea that the increased ratio of amyloid- $\beta$ 42/amyloid- $\beta$ 40 in the brains of patients with Alzheimer disease was meaningful, but, as noted above, all of these candidate drugs failed. Attempts were then made to develop BACE inhibitors that inhibit  $\beta$ -site cleavage, but in June 2018 Eli Lilly/AstraZeneca announced the suspension of development of lanabecestat, a BACE1 and BACE2 inhibitor. Similarly, in April 2019, Merck announced the suspension of developing BACE1/ BACE2 inhibitor, verubecestat, and in September 2019, Eisai/Biogen announced the discontinuation of the development of elenbecestat.

The success of the 18-month Clarity AD phase 3 clinical trial of lecanemab in early Alzheimer disease

(defined as MCI or mild dementia due to Alzheimer disease) and the TRAILBLAZER-ALZ2 phase 3 clinical trial of donanemab are a good news, but there are basic outstanding issues regarding the significance of the effect size in real-world clinical practice.

### IS 18-MONTH PROGRESSION CONTROL SUFFICIENT?

Alzheimer disease is a slowly progressive neurodegenerative disease, and the CDR grading shows slow progression from MCI (0.5) to mild (1), moderate (2), and severe (3) over a period of 10 to 20 years. Given this overall course of Alzheimer disease, the 18-month period studied in the clinical trial is only representative of a small portion of the overall typical stages of the disease. In patients with early Alzheimer disease, the average time to becoming severe is 7 to 17 years (Vermunt, 2019), so 18-month clinical trials in early Alzheimer disease provide limited insight into drug efficacy in relation to the overall disease course and its long-term effects. From this standpoint, some have questioned the 18-month treatment metric of lecanemab (Villain, 2022), and the effect size of the primary endpoint (0.45 points on an 18-point functional and cognitive hybrid scale for dementia severity) in relation to substantial side effects and long-term efficacy. The balance between the primary endpoint (0.45 points on an 18-point functional and cognitive hybrid scale for dementia severity), substantial side effects, and long-term efficacy is an important issue for future study.

These discussions underscore the complexity of translating early clinical trial results for Alzheimer disease into real-world clinical practice and the importance of estimating the long-term therapeutic effects of lecanemab. Although long-term trials that investigate and analyze more practical outcomes (e.g., institutionalization rates and cost of care) have the potential to settle these uncertainties, their duration, cost, methodological bias (withdrawal rates), and ethical issues (delays in obtaining the drug) make long-term trials an unrealistic option.

### DO THERAPEUTIC ANTIBODIES HAVE DISEASE-MODIFYING EFFECTS?

Evaluation of the level of evidence for disease-modifying effects of therapeutic antibodies is important to address some of the above issues. Disease-modifying effects, unlike symptomatic effects, are likely to represent permanent changes in disease progression,

and disease-modifying effects can be demonstrated using a variety of data, including therapeutic effects on mechanisms central to the pathophysiology of Alzheimer disease, biomarker measurements, and clinical trial design (Cummings, 2017).

The amyloid cascade hypothesis postulates that amyloid deposition is the basic pathology, followed by tau pathology and that neuronal degeneration can be a disease-modifying therapy. On the other hand, the potential symptomatic effect of anti-amyloid immunotherapy may also be biological. Restoration of synaptic function through reduction of toxicity of various A $\beta$  species on synaptic transmission (so-called A $\beta$  stress) may underlie the clinical benefit of A $\beta$  clearance.

Recent clinical trials of anti-amyloid immunotherapies demonstrated the ability to remove amyloid beta, and it is possible that these agents may also induce changes in downstream biomarkers that support the amyloid cascade hypothesis and disease-modifying effects. However, changes in fluid biomarkers, such as phosphorylated tau in plasma and cerebrospinal fluid (CSF), should be interpreted with caution because amyloid pathology may directly influence their measurement. Changes in markers of neurodegeneration are unknown, but it was reported in the Clarity AD study that total tau and neurogranin concentrations in spinal fluid decreased and the rate of hippocampal atrophy slowed (Van Dyck, 2023). Conversely, anti-amyloid immunotherapy (with the exception of high-dose gantenerumab) has shown no therapeutic effect on neurofilament light chains in spinal fluid or plasma. Further, accelerated global cerebral atrophy and ventricular enlargement have been reported in almost all phase II and III trials of anti-amyloid antibodies (Ayton, 2021). Future studies with pre-specified mediation analysis are required to clarify these conflicting results, and the association between biomarkers and primary outcomes, such as amyloid PET load clearance, tau PET load kinetics, medial temporal lobe atrophy rate and CDR-SB score (quantitative based on the amyloid/tau/neurodegeneration biomarker model hypothesis).

### VALIDATION OF DISEASE-MODIFYING EFFECTS OF DELAYED START DESIGN

If anti-amyloid antibody therapeutics have disease-modifying properties, the difference between the two groups in a parallel-group clinical trial should gradually increase, and the clinical course of patients receiving anti-amyloid immunotherapy and those

receiving placebo could provide indirect evidence of disease modification. Similarly, the gradient of CDR-SB scores in the Clarity AD trial appears to show that the initial differences tended to widen over the course of the trial, but not beyond 12 months. However, gradient analysis has limitations, and the absence of a discrepancy does not rule out disease modification in the presence of a nonlinear, potential treatment effect.

From the available data, it is not currently possible to determine the disease-modifying effects of anti-amyloid antibody therapy. For clarification, a new trial design using a delayed start design could provide a higher level of evidence for a disease-modifying effect. In such a double-blind trial, patients would be randomly assigned to receive either a placebo or the active treatment in the first phase of the trial. In the second phase of the trial, all patients would receive active treatment. If the study drug has a disease-modifying effect, it is expected that the delayed start group will not catch up to the early start group, and this result would be consistent with a permanent change in clinical course. The requirements for these trials are that there must be no variation in the washout period prior to delayed start, there must be no randomization bias related to the arbitrary nature of unblinded extensions, the blinding must continue during the two stages of the trial, and the analysis of the primary endpoint at the end of each stage must be prespecified. The Clarity AD trial of lecanemab had sufficient power to show a significant difference between the two parallel groups at approximately 6 months and that the anti-amyloid effect appeared to plateau after about 12 months. Thus, a delayed start trial period testing anti-amyloid immunotherapy in early Alzheimer disease could range between 18 and 24 months, comparable with current parallel group trials.

However, delayed start trials have limitations and flaws. For example, differences in dropout rates between the placebo and treatment groups in the first phase may bias the results, especially if the treatment has both symptomatic and disease-modifying properties. Such designs have been used in trials of anti-synuclein immunotherapy in early Parkinson disease (Lang, 2022), demonstrating the ethical, methodological, and financial feasibility of delayed start trials in the early stages of neurodegenerative disease.

It is therefore important to determine whether or not anti-amyloid antibody therapy has a disease-modifying effect through clinical trials. Theoretically, clinical trials with a delayed start design

combined with analysis of pre-specified downstream biomarkers as a primary endpoint could increase the level of evidence for disease. The level of evidence for disease-modifying effects should be increased by clinical trials with a delayed start design combined with analysis of downstream biomarkers with a pre-determined primary endpoint. Increasing the level of evidence for disease-modifying effects would provide useful information for physicians to provide appropriate information to patients and caregivers in the collaborative decision-making process regarding the long-term effects of anti-amyloid immunotherapy in early Alzheimer disease. Such trials are also necessary to confirm the long-term risk-benefit ratio and cost-effectiveness of anti-amyloid immunotherapy in early Alzheimer disease, and will aid health providers and regulators in their decisions.

## RELATIONSHIP BETWEEN AMYLOID PATHOLOGY AND TAU PATHOLOGY

TRAILBLAZER-ALZ 2 was a randomized, double-blind, placebo-controlled phase 3 trial of donanemab in patients with early Alzheimer disease. Subjects showing both A $\beta$  and P-tau deposition by PET were included, and prior to randomization, they were stratified by baseline tau PET into low/medium (68.1%) and high tau (31.8%) groups.

The least squares mean difference in iADRS at 76 weeks was 3.25 points (35.1% progression reduction) in the low/medium tau group and 2.92 points (22.3% progression reduction) in the overall population, a significant difference between the low and high tau groups. Similar treatment effects were observed for all secondary clinical endpoints, with patients with low/medium tau generally showing larger effect estimates than the treatment effect in the overall population. The clinical significance of these effects was assessed by exploratory analysis. While treatment with donanemab reduced the risk of progression from MCI to mild dementia or from mild to moderate dementia, in the low- and intermediate-tau groups, donanemab treatment reduced iADRS and CDR-SB scores by 4.36 and 7.53 months, respectively. Demonstrating the clinical benefit of donanemab in patient-understandable measures, such as change in disease status and time gained, may help inform shared decision-making regarding the significance of the benefit to the individual compared with the risks and costs of treatment. When patients were stratified by baseline tau PET, the low/medium group had larger effect size point

estimates. Conversely, post hoc analysis showed that patients in the high tau group had little clinical benefit compared with the placebo group. Tau staging, in addition to clinical criteria and A $\beta$  biomarker positivity, may therefore be important in identifying patients who would benefit most from A $\beta$ -targeted monoclonal antibody therapy. However, limited access to PET scans for A $\beta$  and tau will make it difficult to implement these methods in clinical practice. Further studies are needed to determine whether blood-based biomarkers can substitute for PET in measuring amyloid lowering and predicting clinical response (Pontecorvo, 2022).

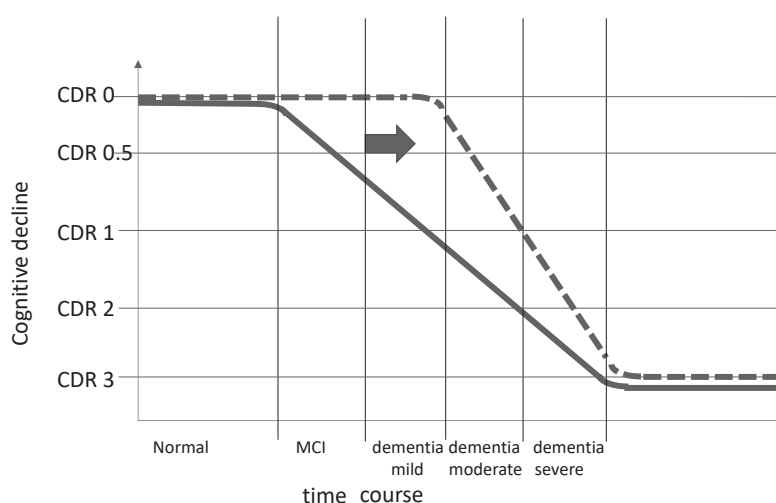
Therapeutic effects on Alzheimer disease biomarkers downstream of A $\beta$  were mixed. Donanemab significantly reduced plasma P-tau217 concentrations, a marker of A $\beta$ -mediated tau phosphorylation and secretion. However, although a significant effect was seen in a phase II study of donanemab (Mintun, 2021; Shcherbinin, 2022), no effect was seen on longitudinal tau PET of frontal cortical regions. Magnetic resonance imaging (MRI) showed that donanemab treatment reduced hippocampal volume but caused greater reductions in whole brain volume and ventricular volume expansion. This is a paradoxical effect reported with other A $\beta$ -targeted monoclonal antibodies, which does not appear to reflect the degree of neurodegeneration or to be associated with clinical decline (Barkhof, 2023). More detailed analysis of biomarker data is needed to assess evidence of downstream disease modification and to evaluate

the relationship between biomarker changes and clinical outcomes.

## CLINICAL APPLICATION OF DISEASE -MODIFYING THERAPY

In the near future, when antibody therapeutics targeting amyloid- $\beta$  for Alzheimer disease come into clinical use, outpatient infusion therapy every two or four weeks will be a reality in the treatment of Alzheimer disease. Like outpatient treatment with anticancer drugs, intravenous therapy will begin with adequate preparation for various possible side effects, and medical care for ARIA and other complications may be more intensive than ever before. Establishing a system that can provide all people with medical care and requires time, resource and personnel intensive administration of regular intravenous therapies is a significant challenge.

Antibody therapeutics are thought to have the potential to slow the rate of cognitive decline in the early stage of Alzheimer disease, thus prolonging the duration of mild disability (Figure 4). The progression of the disease stage after extensive administration of antibody therapeutics in terms of all stages of Alzheimer disease until the severe stage is still uncertain. Although disease-modifying drugs inhibit the progression in the early stage for a period of time, cognitive function may decline rather more rapidly than in non-drug-treated individuals after a certain threshold is exceeded. In this regard, there



**Figure 4. Effects of disease-modifying therapy to clinical development of Alzheimer disease**

Progression of clinical stage is delayed by disease-modifying therapy (DMT) in the early stage of Alzheimer disease. While the clinical trials have revealed the delay of symptom progression during 18 months periods, it is to be studied whether the advanced symptom will be also delayed or not.

may be various approaches to evaluation of this clinical benefit.

### INVESTIGATION OF PATHOLOGICAL MODIFICATION EFFECTS WITH CONSIDERATIONS OF COGNITIVE RESERVE

Both lecanemab and donanemab are anti-amyloid antibody drugs and have the ability to remove amyloid from the brain. For progression of clinical symptoms, the CDR-SB score in the CLARITY-AD trial was 1.21 points lower in the lecanemab group versus 1.66 points lower in the placebo group, a difference of 0.45 points. In the TRAILBLAZER-ALZ 2 trial, dementia severity worsened by 1.72 points over 18 months in the donanemab group versus 2.42 points in the placebo group, a difference of 0.7 points. Donanemab can delay progression by 3-6 months, but the degree of this progression suppression varied with the degree of tau pathology, with 47% of the low/medium tau group stable on CDR-SB at 1 year (vs. 29% in the placebo group). These results are clinically meaningful because they indicate that anti-amyloid- $\beta$  antibody therapy can delay disease progression and keep more patients in the MCI and mild dementia stages longer.

The pathological process of Alzheimer disease is complex and is defined not only by amyloid- $\beta$  deposition in the brain parenchyma and cerebral vessel walls and tau deposition in neurons and nerve fibers, but also by various biological factors. Anti-oxidant, anti-chaperone, anti-endoplasmic reticulum (ER) stress, and anti-apoptotic effects, for example, may be considered just as candidates for Alzheimer drugs of disease-modifying effects, as mentioned above. In addition, anti-inflammatory, anti-diabetic, and anti-hyperlipidemic mechanisms may also affect the

pathogenesis of Alzheimer disease. Considering the definition of dementia as the impaired ability to remember, think, or make decisions that interferes with doing everyday activities, psychosocial factors may influence the progression of Alzheimer disease.

Against this background, the concept of cognitive reserve should be extensively discussed, which is hypothesized as the ability to antagonize brain aging and pathology and to inhibit cognitive decline (Stern, 2009; Takeda, 2012). People with a high level of education, people who have worked in intellectual occupations, and people who have maintained an active mental life even in old age are known to have a high cognitive reserve, which keeps comparatively lower rate of developing dementia at an advanced age. However, the nature of cognitive reserve has not yet been fully elucidated (Takeda, 2022), people with high cognitive reserve tend to have a longer time to develop dementia, suggesting higher cognitive reserve helps maintaining high cognitive function up to a certain level by antagonizing the pathology in the brain. However, once cognitive decline begins, the rate of decline is faster for those with high cognitive reserve than for those with low cognitive reserve (Figure 5).

Antibody therapeutics for Alzheimer disease have been shown to slow the progression of cognitive decline and disease staging during the beginning of the disease. However, it would be unrealistic to assume that the effect would be observed throughout the duration of dementia, although the rate of cognitive decline after the onset of the disease stage requires clarification. Assuming that the periods leading up to severe dementia are approximately concurrent, it is possible that the rate of cognitive decline after the onset of cognitive decline may be faster for those using therapeutic antibodies.

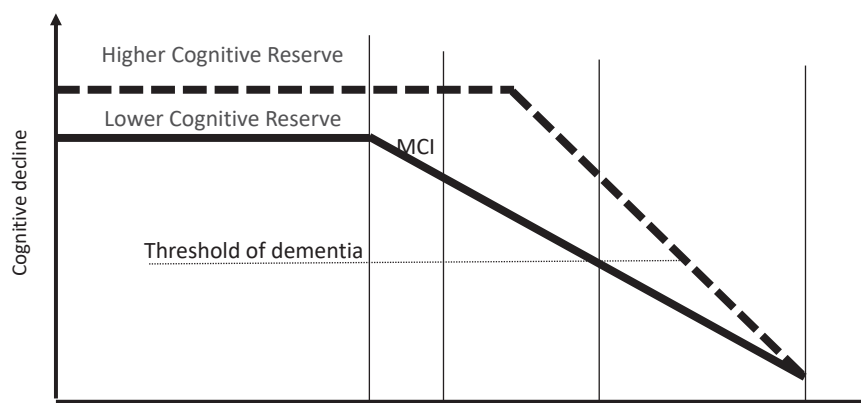


Figure 5. Effect of cognitive reserve on the onset and progression rate of dementia.

Given the complexity of the pathology of cognitive decline in Alzheimer disease and the rather minimum effects of donanemab and lecanemab on cognitive function and the rate of decline in cognitive measures, it is important to actually test the effects of these agents separately in groups with higher and lower cognitive reserve. Given that individuals with high cognitive reserve are able to antagonize the progression of amyloid- $\beta$  deposition in the brain to a certain threshold, and that they are less likely to develop dementia, it is conceivable that anti-amyloid antibody therapeutics may be more effective than in individuals with low cognitive reserve.

### COGNITIVE REHABILITATION AIMING FOR INCREASE IN COGNITIVE RESERVE

The pathogenesis of Alzheimer disease is closely related with brain aging, and the 65% of the risk is regarded nonmodifiable, which still leaves 35% of modifiable risks for late life dementia (Livingston, 2017). The modifiable risk factors include hearing loss, hypertension, and obesity in midlife, and smoking, diabetes, depression, inactivity, and social isolation in late life. Livingstone (2017) states that 35% of these risk factors can be remediated by modifying the life style in middle and later life. This finding supports the idea that dementia, including Alzheimer's disease, is not necessarily inevitable.

Cognitive reserve is also useful in preventing

dementia, and interventions to maintain cognitive reserve are now under investigation. Although the biological nature of cognitive reserve has not been clarified, writing ability in youth, high educational background, intellectual occupation, hobbies, exercise habits, interaction with others, social participation, and purpose in life, and others are shown to increase cognitive reserve.

Interventions to prevent the onset of dementia will be more important than ever in Alzheimer's disease treatment after the introduction of antibody therapeutics. It is an important issue to study therapeutic antibodies and psychosocial interventions to enhance cognitive reserve may work to prevent the disease onset in synergy with each other.

A wide variety of psychosocial interventions are being tried for patients with Alzheimer's disease. Recollection therapy, reality disorientation training, and aroma, psychodrama, horticultural, animal assisted therapies are popular examples. Physical exercise, gymnastics, ball games, music, humanitude, and others have been tried as part of the rehabilitation intervention. At day service centers in Japan, exercise, walking, and indoor occupational therapy such as games, music, painting, and paper crafts are popular, but there is insufficient evidence for any of these interventions.

The most important issue for rehabilitation professionals is the prevention of onset and progression of dementia. Figure 6 shows the possible contributions

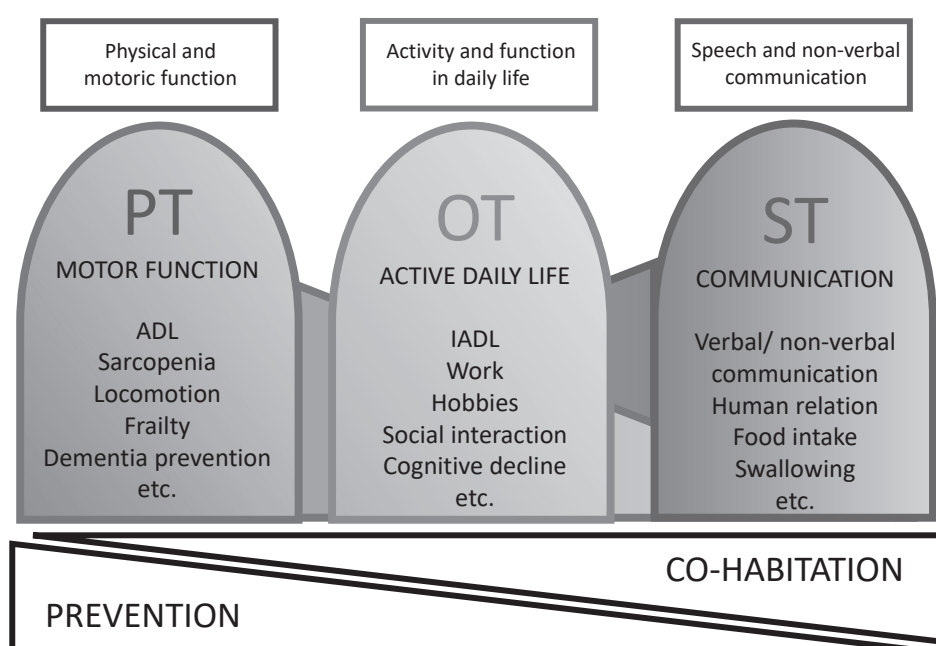


Figure 6. Role of rehabilitation for dementia patients

of physical therapists, occupational therapists, and speech-language pathologists to people with dementia, their families, and society. Rehabilitation that also incorporates psychosocial factors is said to prevent the onset of dementia as well as cognitive reserve. However, it is unknown how such rehabilitation interventions can modify the rate of cognitive decline once it has begun to progress. At best, it may delay the onset of dementia and slow the rate of cognitive decline to the same degree as in the natural course of the disease without the use of drugs.

## CONCLUSION

Anti-amyloid- $\beta$  antibody therapies for Alzheimer's disease in Japan are desirable, but many challenges remain. The primary safety concern is ARIA, which appears with considerable efficiency as edema, exudates or bleeding. In the treatment group, the risk of ARIA-E has also been shown to be high, suggesting that anti-amyloid- $\beta$  antibody therapeutics could be used to assess the risk of ARIA. While ARIAs are generally managed safely in clinical trials, anti-amyloid- $\beta$  antibody therapy should be cautiously introduced into clinical practice, for example, by excluding patients with significant cerebral amyloid angiopathy on baseline MRI, performing periodic surveillance MRIs during treatment, and/or incorporating a conservative algorithm to suspend or stop treatment if there is ARIA. For now, a registry could be used to track adverse events and clinical outcomes over time.

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