Review Article

Development of Monoclonal Antibody Therapeutics for Alzheimer's Disease

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Abstract

Background: In a previous review article in *the Taiwanese Journal of Psychiatry* (Takeda and Tagami: *Taiwanese J. Psychiatry* 2020; 34: 152-61), we gave the development status of drugs for Alzheimer's disease, presented a relatively pessimistic view, and highlighted the difficulties in their development. **Methods:** Since I have witnessed some encouraging development of monoclonal antibody therapeutics against Alzheimer's disease, I have decided to contribute this article. I reviewed new data from published journals and from internal reports of pharmaceutical companies. I have also offered some explanations and comments. **Results:** In 2021, I saw promising clinical trial results reporting the use of aducanumab, a monoclonal antibody treatment against amyloid β protein, and the U.S. Food and Drug Administration (FDA) announced a decision for expedited approval of aducanumab. But the results of aducanumab's phase III clinical trials were considered by some to be insufficient for the approval, and the FDA's decision was controversial. The European and Japanese regulatory authorities did not approve aducanumab. In September 2022, however, more promising results were announced from Phase III clinical trials of another monoclonal antibody, lecanemab. **Conclusion:** In this review, I have recounted the state of the arts of drugs for treating dementia and highlighted remarkable recent progress in the development of monoclonal antibody therapeutics for Alzheimer's disease.

Key words: aducanumab, immunotherapy, lecanemab, memory impairment
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Introduction

The development of monoclonal antibody therapeutics for Alzheimer's disease has undergone significant progress since our last review article [1], which has made me to contribute the revised review on anti-Alzheimer drug developments, especially those in these two years.

At present, there are 40 million patients with dementia worldwide, 60%-70% with Alzheimer's disease. The pathology of Alzheimer's disease is closely related to brain aging, and as the average life expectancy increases, the number of patients with dementia is expected to double every 20 years, reaching 115 million worldwide by 2050. [2]. To combat problems with dementia, some developed countries are taking nationwide measures, such as the National Dementia Strategy in the United Kingdom and the National Alzheimer's Plan in the United States of America. In Japan, where the population has been aging at the fastest pace in the world, the "National Dementia Strategy" was announced in June 2018, aiming at realizing a society where people with dementia can continue to live as they like in a good community environment as long as possible [3]. The basic concept is to focus on prevention and coexistence, and it states that measures should be promoted with careful consideration of the viewpoints of people with dementia and their families. The aim is at creating a society in which the onset of dementia is delayed, and people can live their daily lives with hope, even after they have dementia [4].

Brief History of Drug Development for Alzheimer's Disease

Alzheimer's disease is perhaps the most challenging disease to overcome in the 21st century due to the large

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number of patients, the long duration of the disease, and the severity of the disorder. Development of a cure for the disease is arguably the greatest challenge to be addressed in modern medicine.

The first case report patient, Auguste Deter, by Alois Alzheimer in 1906 was what we now refer to as "young-onset Alzheimer's disease," and initially Alzheimer's disease was distinguished from senile dementia. More recently, both young-onset and old-onset forms of the disease are understood to share the same basic pathology of senile plaques, neurofibrillary tangles, and neuronal loss, so have collectively become referred as Alzheimer's disease.

The pathogenesis of Alzheimer's disease has been vigorously studied since the 1980s, and at a molecular level, it has been gradually elucidated. The amyloid beta protein that constitutes the senile plaques and the excessively phosphorylated tau protein that constitutes the neurofibrillary tangles within neurons and around the senile plaques have been identified.

In the review published in 2020 [1], the developmental stages of anti-Alzheimer drugs were classified into three levels: (level 1) drugs for improving cerebral circulation/ metabolism, (level 2) symptomatic drugs, and (level 3) disease-modifying drugs [1]. The development of anti-Alzheimer drugs progressed in 2021. Aducanumab, a monoclonal antibody against amyloid beta protein, was granted expedited approval by the US Food and Drug Administration in 2021, which can be classified as preemptive drugs in between level 2 and level 3 of the previous classification. In this paper, we propose a revised classification of anti-Alzheimer drugs into four levels, now including the class of preemptive drugs which was pioneered by aducanumab and other monoclonal antibody therapeutics will likely be included in this class (Figure 1).

- Level 1 includes many nootropics developed in 1960-80s which aimed for improvement of cerebral metabolism and blood circulation. They were once frequently prescribed to treat dementia including Alzheimer's disease, but after re-evaluation in 1999, the use of many drugs that improve cerebral metabolism has been discontinued because clinical benefit could not be adequately demonstrated.
- Level 2 drugs are those targeting neurotransmitters, hormones, or neurotrophic factors. Acetylcholinesterase inhibitors came into clinical use, aiming to inhibit the degradation of acetylcholine, which is reduced in brains with Alzheimer's disease. Tacrine, the first drug, was not widely used due to its hepatotoxicity, but cholinesterase inhibitors such as donepezil (approved in the U.S. in 1996 and in Japan in 1999), galantamine, and rivastigmine have become widely used throughout the world. Subsequently, the *N*-methyl-D-aspartate antagonist memantine was developed (approved in Europe in 2002, in the U.S. in 2003, and in Japan in 2011). These drugs are symptomatic

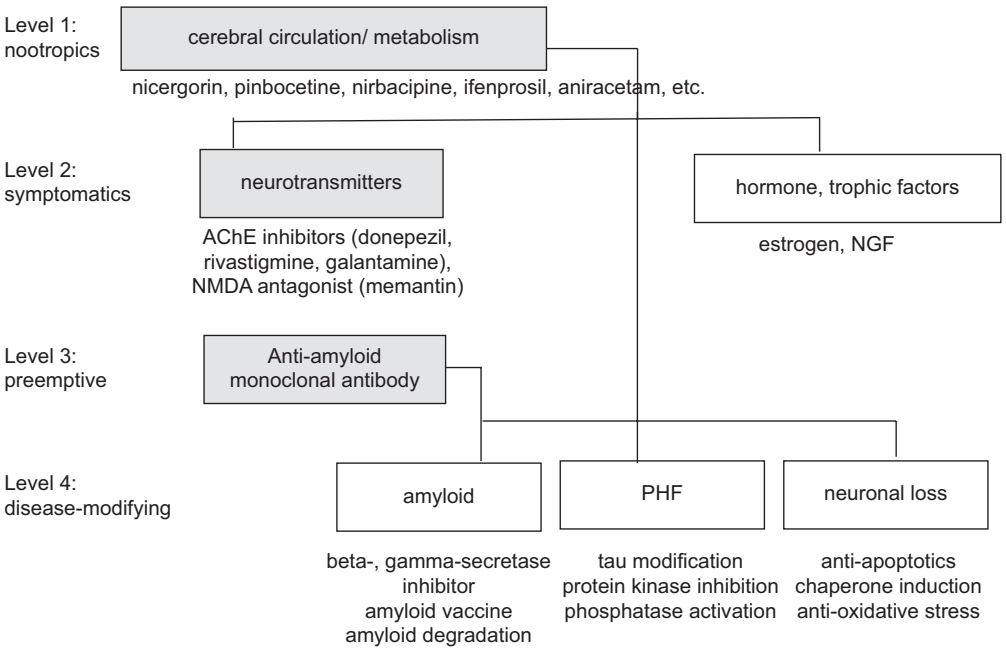

Figure 1. Developmental level of anti-Alzheimer drugs. Drugs available in clinical settings are in black letters, and the drugs not yet developed for clinical use are in red letters. Level 1 drugs were used to improve cerebral circulation and/ or cerebral metabolism until late 1990s. Most of these drugs, however, were abandoned in 1996 because no clinical benefits were confirmed by reevaluation. Level 2 drugs include those targeting neurotransmitters, hormones, and neurotrophic factors. Acetylcholine esterase inhibitors (donepezil, rivastigmine, and galantamine) and NMDA antagonist (memantine) are presently prescribed in most countries to treat patients with Alzheimer's disease. Level 3 drugs are monoclonal antibody therapeutics including aducanumab, lecanemab and others. Aducanumab was granted expedited approval by FDA in 2021. Level 4 drugs are not yet used in clinical settings. Drugs targeting amyloid (aiming for reduced production, reduced aggregation, and/ or increased clearance), paired helical filaments (PHF; reduced aggregation of tau, reduced protein kinases, increased phosphatases), and neuronal loss (anti-apoptosis, chaperone induction, anti-oxidase stress) are under development.

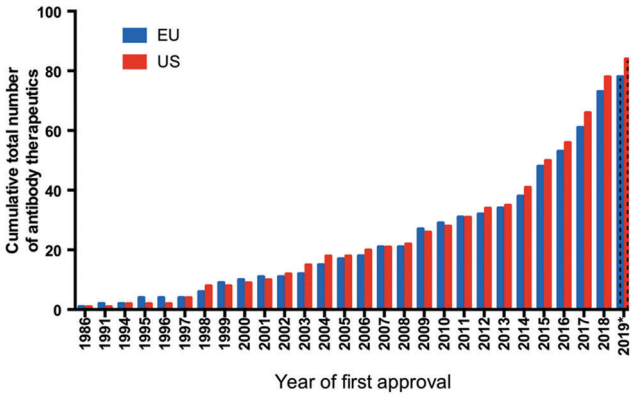

Figure 2. Cumulative number of antibody therapeutics approved by US and European Agency. Adapted from: Kaplon H, Reichert JM: Antibodies to watch in 2021. *mAbs*, 2022; 13: 1860476 [7].

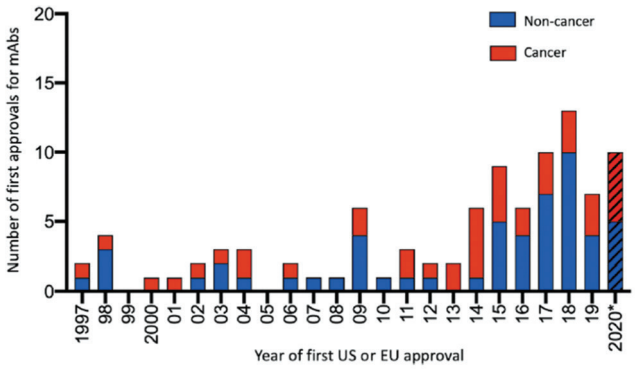

Figure 3. Number of first approvals of monoclonal antibody against cancer and non-cancer disorders. Adapted from: Kaplon H, Reichert JM: Antibodies to watch in 2021. *mAbs,* 2022; 13: 1860476 [7].

treatment; however, the disease progresses even when patients are treated with them. Disease-modifying drugs that can inhibit the progression of Alzheimer's disease are therefore greatly sought after (Figure 2).

- Level 3 drugs are added in this revised scheme, because aducanumab has been granted expedited approval in 2021 for the first monoclonal antibody therapeutics against Alzheimer's disease. As will be described later, lecanemab and other monoclonal antibodies will be approved as preemptive therapeutics to Alzheimer's disease in near future.
- Level 4 anti-Alzheimer drugs are those to modify the disease process itself, which has been tried for more than 25 years without success. The molecular component of neurofibrillary tangles is identified as overphosphorylated tau protein. An amyloid beta (Aβ) protein deposited in the core of senile plaques has been sequenced, which is produced from its precursor, amyloid-beta precursor protein (APP), by the action of beta-secretase and gamma-secretase. In familial Alzheimer's disease with APP mutations, the ratio of Aβ42/Aβ40 is elevated, and such an increase in long Aβ is also observed in patients with Alzheimer's disease with presenilin-1 and presenilin-2 mutations [5]. These findings led to the widespread acceptance of the amyloid cascade hypothesis as the basic pathology of Alzheimer's disease [6]. The amyloid cascade hypothesis has been the main focus in the development of amyloid modifying agents, but neither β-secretase inhibitors, γ-secretase inhibitors, nor γ-secretase modifying agents have been successful.

Development of Immunotherapy and Antibody Therapy

Recently, the number of biological agents has been increasing in drug development, especially in antibody therapies. Figure 3 shows the transition of antibody therapeutics first approved by the European Medicine Agency (EMA) and the U.S. Food and Drug Administration (FDA) since 1986, when the first antibody therapeutics were developed, mostly for cancer [7]. Since 2015, the number of antibody therapeutics for diseases other than cancer has been increasing owing to the growing understanding of pathogenesis of many diseases in molecular basis. As of 2020, about 40 products have been developed in oncology and a similar number of products have been developed in nononcology areas, with approval of approximately 80 products [8]. Antibody drugs under review outside of oncology in 2020 are listed here with the target molecule and target disease in parentheses: tanezumab (NGF, osteoarthritis pain), narsoplimab (MASP-2, hematopoietic stem cell transplant-associated thrombotic microangiopathy), evinacumab (angioprotein-like protein 3, hypercholesterolemia), aducanumab (amyloid beta, early Alzheimer's disease), tralokinumab (IL-13, atopic dermatitis), teplizumab (CD3, type 1 diabetes), inolimomab (CD25, acute graft-vs-host disease), ansuvimab (Ebola virus, Ebola virus infection), bimekizumab (IL-17A and IL-17F, psoriasis), anifrolumab (IFNa,b, ω receptor 1, systemic lupus erythematosus), sutimlimab (C1s, cold agglutinin disease). Notably, aducanumab was included in this list as the first antibody treatment for early Alzheimer's disease.

Beginning of Amyloid-β (Aβ) Immunotherapy

In 1999, Shenk et al. (Elan) reported that administration of Aβ to Alzheimer's disease model transgenic (TG) mice significantly reduced amyloid deposition in the brain [9]. This had a major impact because the cerebral immune system had been thought to be independent from the peripheral immune system. Plaque formation consisting of amyloid in the brain, neurite degeneration, and astroglial proliferation were suppressed in mice immunized with Aβ at a young age, the progression of pathological changes (e.g., amyloid deposition in the brain) was markedly suppressed, and the amyloid plaques in the brain were reduced or even disappeared in aged mice [9]. Aβ vaccine therapy for mice with high APP expression was shown to be effective in suppressing age-related decline in learning and memory ability [10, 11].

Based on the results of these animal studies, Elan conducted a clinical trial of AN1792, a vaccine consisting of monoclonal antibody against Aβ1-42 and an adjuvant (QS-21). A Phase I study of the AN1792 vaccine was conducted in the U.S. and the United Kingdom in 2000 for patients with mild to moderate Alzheimer's disease, followed by a Phase II trial in 2001. In 2002, the AN1792 trial had to be terminated due to aseptic meningoencephalitis observed in 6% (18 of 300) of vaccine-treated patients in this Phase II trial.

Development of meningoencephalitis was the biggest problem with AN1792, and it became necessary to examine how to develop a vaccine without this side effect. The mechanism of meningoencephalitis caused by vaccination was thought to be based on the activation of Th1-type CD4-positive cells that respond to Aβ, and it was widely believed that the Aβ sequence, which has a low activation capacity of T cells involved in cellular immunity and activates B cells (Th2 response) to produce antibodies, was preferable. Th1 T cell activation is known to be more likely to be induced on the *C*-terminal side of Aβ, while Th2 reaction is more likely to be induced on the *N*-terminal side, leading to the development of Aβ vaccines using the *N*-terminal part of Aβ sequence in subsequent immunotherapy [12].

Although the meningoencephalitis outbreak resulted in the discontinuation of the trial with only 1-3 doses of the vaccine, the trial was still informative. Blood IgG antibody titers to Aβ increased up to 2,200-fold in approximately 20% of patients treated with AN1792, and there was a trend toward decreased cerebrospinal fluid tau in this response group. Various cognitive function tests failed to show significant improvement, but there was a significant improvement in the general functional analysis with neuropsychological test battery. Elsewhere, in an autopsy of a person who died in a traffic accident after receiving AN1792, senile plaques in the brain were shown to be removed, and microglia were accumulated in the area where senile plaques had disappeared, and T cells were accumulated around the blood vessels in the meninges [13].

Types and Mechanisms of Amyloid-β Immunotherapy

Immunotherapy can be broadly classified into two types: vaccine therapy (active immunotherapy) in which antigens are administered, and antibody therapy (passive immunotherapy) in which antibodies are administered. Vaccine therapy and antibody therapy differ in that antibody therapy is less likely to cause meningoencephalitis, which remains a concern with vaccines, and it can be expected to be effective for non-responders who are less likely to produce antibodies by vaccines. However, considering manufacture, vaccine therapy generally has the advantage of shorter development time and lower costs. Most of the vaccine therapies under investigation use the *N*-terminal sequence of Aβ with the aim of avoiding the meningoencephalitis observed in the AN1792 trial, while retaining the ability to produce anti-Aβ antibodies. For example, the monoclonal antibody at the most advanced stage of clinical evaluation, ACC-001 (Elan/Weiss) used Aβ1-7 sequence and CAD-106 (Novartis) used the Aβ1-6 sequence binding a carrier substance to the N-terminal sequence of Aβ as a device to increase antigenicity.

Various antibodies to be used in therapy have been widely investigated. First, with regard to epitopes, antibodies that recognize the N-terminal, intermediate, and C-terminal sequences of Aβ have been developed. Bapineuzumab (Elan/Weiss, AAB-001) is a humanized anti-Aβ antibody that recognizes the *N*-terminal sequence of Aβ, solanezumab (Eli Lilly, LY2062430) recognizes the middle sequence of Aβ, and PF-04360365 (Pfizer) recognizes the C-terminal region of Aβ.

Four hypotheses have been proposed regarding the mechanism of action of Aβ antibodies [14]. The first is that antibodies enter the brain through the blood–brain (BBB), they bind to amyloid aggregates in the brain, and are then phagocytosed by microglia in the brain via the Fc receptor. The second hypothesis is that antibodies can be absorbed into the bloodstream via the BBB. The third hypothesis is that antibodies migrate from the blood into the brain through the BBB and dissolve Aβ from amyloid aggregates in the brain, thereby inhibiting further aggregation. The fourth hypothesis is that antibodies will draw Aβ from the blood into the brain and transfer it without penetrating the BBB. Solanezumab (Eli Lilly) has been developed with this idea in mind (Figure 4) [15].

Amyloid-β Antibody Therapy

The earliest development of antibody therapy for Alzheimer's disease was bapineuzumab (Elan/Weiss) and solanezumab (Eli Lilly). A phase II study of bapineuzumab was conducted in 234 patients with mild to moderate Alzheimer's disease by administering four doses of bapineuzumab (0.15, 0.5, 1.0, and 2.0 mg/kg) intravenously six doses every 13 weeks over an 18-month period. Adverse events, angiogenic edema on MRI, were observed in 12 bapineuzumab-treated patients, 10 of whom carried the apolipoprotein E4 allele. Efficacy on endpoints was evaluated by ADAS-cog (Alzheimer's Disease Assessment Scale- cognitive), NTB (Neuropsychiatric Test Battery), CDRSB (Clinical Dementia Rating Sum of Boxes), MMES (mini-Mental State Examination), cerebrospinal fluid tau, and MRI brain volumetry, and was analyzed separately for ApoE4 carriers and noncarriers. Efficacy trends were observed for ADAS-cog and NTB in the overall population. In the ApoE4 nonpositive group, statistically significant and clinically meaningful effects were observed in several endpoints, indicating that efficacy was higher in ApoE4-negative patients than in ApoE4-positive patients, and that the ApoE4-negative group also showed a reduction in brain volume reduction. Based on the results of the Phase II trial, a Phase III trial was conducted with different doses for ApoE4 carriers and noncarriers, but the results were unsatisfactory and the development was halted.

Beginning in 1992, all drug discoveries for Alzheimer's disease have been followed by a series of failures in Phase

III trials, leading to widespread pessimism toward the discovery of disease-modifying drugs for Alzheimer's disease. Although molecular pathology has been elucidated to some extent, many drugs have been developed based on such pathological hypotheses with preclinical studies confirming efficacy, but many candidates have failed to show efficacy in clinical trials.

Exactly how to understand the discrepancy between animal studies and human clinical trials has therefore been widely debated. The following issues have been discussed: (a) the amyloid cascade hypothesis may be incorrect, (b) amyloid removal may not necessarily lead to improvement of clinical symptoms, and (c) the method of human clinical trials may be incorrect [16]. The framework of clinical trials for the development of disease-modifying drugs for Alzheimer's disease has also significantly changed. However, in a newly proposed framework for clinical trials, subjects are selected using biomarkers before the onset of the disease, with examination of the efficacy of the drug in reducing the transition from high-risk patients to actual development of dementia. To investigate the effect of drugs on reducing the transition from high-risk to dementia, the new framework of findings is to use biomarkers to select subjects before the onset of the disease. New clinical trial frameworks require detailed data collection, including amyloid PET, genetic testing, biomarker quantification, and cognitive assessment to correctly select high-risk patients, and they also require inclusion of high-risk populations of several hundred patients and a long observation period of at least 3-4 years. Several AD antibody therapies are being investigated on such platforms (Table 1).

Development of Aducanumab

Aducanumab is a recombinant human IgG1 antibody produced by Neurimmune from a library of peripheral blood lymphocytes from cognitively normal elderly patients, which was sold to Biogen in 2007 and has been under investigation. Aducanumab binds to both soluble and insoluble Aβ, but is more than 10 000-fold selective for Aβ polymerization. It has an epitope in the Aβ3-7 region and is thought to bind selectively to oligomers and fibrils [17]. In preclinical studies using a TG animal model of Alzheimer's disease (Tg2576), aducanumab reduced Aβ plaques in the brains of young animals (aged 9 months) in a dose-dependent manner, but did not reduce Aβ in older animals (aged 22 months). This suggests that aducanumab inhibits Aβ polymerization rather than removing Aβ that is present. Aβ reduction was not linked to improved cognitive function in animal studies.

In 2016, a P1a clinical trial (NCT01397539) was conducted

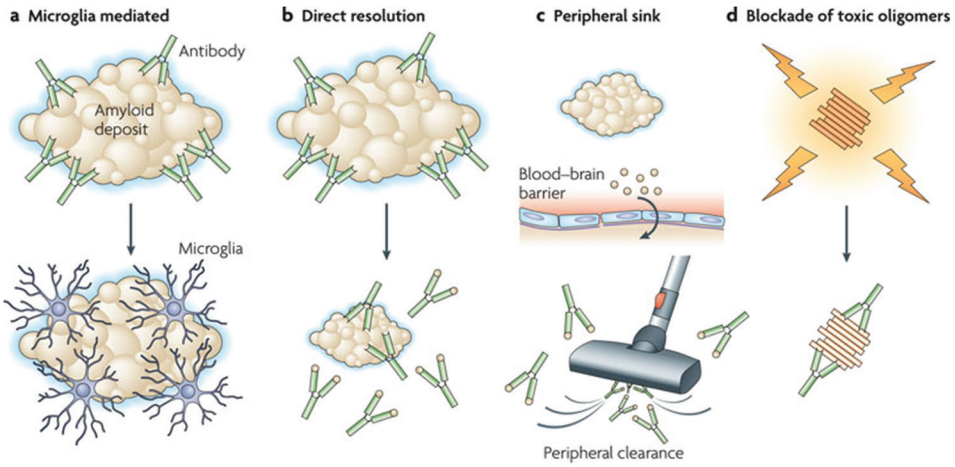

Figure 4. Hypothetical mechanisms of amyloid removal. Adapted from: Citron M: Alzheimer's disease: strategies for disease modification, *Nature Reviews Drug Discovery* 2010; 9: 387–398 [15].

Table 1. Properties of selected anti-Aβ antibodies currently tested in clinical trials for Alzheimer's disease

mAb clinical candidate	Mouse antidody anlog	Clinical stage and status	Aβ selectivity (monomer, aggregate)	Epitope (residues)	Sponsor
Aducanumab	Aducanumab	Phase III, enrolling by invitation	A > > M	3-7	Biogen Inc.
Lecanemab (BAN2401)	mAb158	Phase III, recruiting	A > > M	1-16	Biogen Inc. and Co.
Solanezumab	M266	Phase III, recruiting	M > > A	16-26	Eli Lilly and Co.
Crenezumab (MABT5102A0)	MABT5102A	Phase III, terminated	A = M	13-24	Genentech Inc.
Donanemab	mE8-IgG2a	Phase II, recruiting	A > M	*N*-terminal pyroglutamate	Eli Lilly and Co.
Gantenerumab	Gantenenmab	Phase III, recruiting	A > M	3-11, 18-27	Hoffman-LaRoch

on 53 patients with Alzheimer's disease. Low doses of aducanumab (≤ 30 mg/kg) produced no side effects (SAEs), while high doses of aducanumab (60 mg/kg) produced amyloid-related imaging abnormalities (ARIAs). Interestingly, plasma Aβ40 and Aβ42 were elevated in patients receiving 60 mg/kg aducanumab for 3 weeks, suggesting that high-dose aducanumab binds to and withdraws soluble Aβ monomers. However, 24 weeks after treatment, the 13-item Alzheimer's disease Assessment Scale-Cognitive (ADAS-Cog13) showed no significant difference in cognitive function.

The subsequent P1b clinical trial, PRIME (NCT01677572), showed that PET significantly reduced brain Aβ levels in patients with prodromal to mild Alzheimer's disease. Monthly aducanumab treatment was continued for one year, and the brain Aβ reduction was dose- and time-dependent, and was significantly reduced on PET in patients with prodromal to mild Alzheimer's disease, as measured by the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB). The progression of clinical symptoms was significantly delayed at 1 year compared with placebo.

These results led to two large Phase III trials, ENGAGE (NCT02477800) and EMERGE (NCT02484547). Both trials were conducted for mild cognitive impairment (MCI) and mild dementia due to Alzheimer's disease, with CDR-SB as the primary endpoint. The original plan was to file for FDA review in 2020, but in March 2019, Biogen announced the results of an interim evaluation of both trials. The EMERGE trial showed promising trends, but the ENGAGE trial was discontinued because improvement was unlikely to be shown in the primary endpoint. This interim analysis was based on data from 1748 patients who had completed 18 months of clinical trials by the end of 2018, but it was determined that it would be difficult to achieve the primary endpoint in either trial.

However, in October 2019, Biogen announced that it had analyzed data from 3285 controls and found that the high-dose aducanumab (100 mg/kg) was beneficial in both trials, and that it would file for FDA review. In the EMERGE trial, CDR-SOB scores at week 78 showed significant improvement in the high-volume group compared with the placebo group (22% vs. placebo, $p = 0.01$), as well as in MMSE (18% vs. placebo, $p = 0.06$ being nonsignificant), ADAS-cog (27% vs. placebo, $p = 0.01$). Biogen reanalyzed the data from the discontinued trial and found that the original dose was too low, claiming that the EMERGE trial had shown clinical benefit [17]. The announcement was based on the conclusion that a statistically significant benefit was found for high-dose aducanumab treatment in reducing symptom progression in patients with early Alzheimer's disease [18]. Biogen filed for FDA approval of aducanumab, but there were many who took issue with this filing and had strong opinions concerning the application.

The results of the analysis of aducanumab were presented to the FDA Expert Committee on November 6, 2020, and many members were of the opinion that the results of this analysis were inadequate. Their discussion was summarized in the following four issues: (a) "Is Study 302 (EMERGE) sufficient evidence for the efficacy of aducanumab as a treatment for Alzheimer's disease when viewed independently of Study 301 (ENGAGE)?" (Vote: 1 for, 8 against, 2 withheld); (b) 'Does the PRIME trial provide evidence to support the therapeutic efficacy of aducanumab?' (Vote: 0 for, 7 against, 4 withheld); (c) "Does the PRIME study provide sufficient evidence for the pharmacodynamic efficacy of aducanumab for the pathophysiology of Alzheimer's disease?" (Vote: 5 in favor, 0 opposed, 6 withheld); (d) "When the results of the exploratory analyses of Trial 301 and Trial 302 are considered together with Trial 103 and its pharmacodynamic effects on the pathophysiology of Alzheimer's disease, do you believe that the results of Trial 302 demonstrate the efficacy of aducanumab as a treatment for Alzheimer's disease?" (Vote: 0 in favor, 10 opposed, 1 withheld).

This summary shows that the majority of the experts were negative about the approval of aducanumab, probably because it was different from previous presentations and incompatible with the principle that clinical trials should be based on predefined endpoints to determine efficacy.

A public hearing was held on December 5, 2020, against aducanumab. The British Alzheimer's Association raised doubts about its usefulness, but the American Alzheimer's Association strongly urged the FDA to approve it. Following this hearing, the FDA was supposed to reach a decision by March 2021, but that decision was delayed, and on June 8, 2021, the FDA issued an expedited conclusion of approval for aducanumab. This was an unusual decision, although the FDA has made decisions in the past that have differed from the group opinion of the Expert Committee.

While the FDA decided to grant expedited approval, there were many reservations about this decision. For example, Knopman et al. argued that the results of post hoc analyses were often inaccurate and that further data were needed for FDA approval, requiring at least 78 weeks of additional clinical trials on high-dose aducanumab (www.investors.biogen.com/news-releases/newsrelease-details/biogen - and-eisai-discontinue-phase-3-engage-andemerge-trials). The decision to grant expedited approval was made by the FDA's Peripheral and Central Nervous System Drugs Advisory Committee. According to press reports on June 13, 2021, three of the 11 experts who served on the FDA's Peripheral and Central Nervous System Drugs Advisory Committee resigned because they were strongly against granting expedited approval. One of them was quoted as saying, "This expedited approval is probably the worst decision in the recent history of drug approvals in the U.S." This decision has caused significant controversy.

Many experts have pointed out that aducanumab was expedited for approval based on the surrogate endpoint of 'reducing amyloid beta (Aβ)' without sufficient evidence regarding of its clinical benefit of 'reducing cognitive decline', which is considered to be important for patients and their families. Aducanumab was approved on the basis of the surrogate endpoint of reducing amyloid-β (Aβ). There is currently no clear evidence that a reduction in Aβ will reduce

cognitive decline, and of course, this important point must be clarified in the coming years.

The FDA's expedited approval of aducanumab is conditional. Expedited approval is a mechanism for approving drugs for serious or life-threatening conditions based on surrogate endpoints that are predictive of clinical benefit. In the case of aducanumab, the expedited approval was based on the results of two phase III trials that showed a dose- and time-dependent reduction in Aβ deposition in the brain as assessed by amyloid PET. However, reduction of Aβ in the brain is a surrogate endpoint, not a clinical endpoint of suppression of cognitive decline. In granting expedited approval for aducanumab, the FDA explained that the reduction in Aβ is expected to provide clinical benefit to patients, but that a validation study is a requirement for approval to confirm that clinical benefit. If the validation study does not demonstrate clinical benefit by February 2030, the approval will be revoked.

Use of Aducanumab

Following the aforementioned process, aducanumab was rapidly approved by the FDA under the trade name Aduhelm. Aduhelm is administered every 4 weeks by approximately 1-hour intravenous infusion, starting at 1 mg/kg for the first and second doses, titrating to 3 mg/kg for the third and fourth doses, 6 mg/kg for the fifth and sixth doses, and 10 mg/kg for the seventh and subsequent doses. Monitoring for amyloid-related brain imaging abnormalities (ARIA) is required for Aduhelm infusion therapy. A brain MRI scan taken within one year prior to the start of treatment is required, as well as MRIs before the 7th (before the start of the maintenance dose) and 12th (after six maintenance doses) doses. If more than ten new microhemorrhages or three or more brain surface iron deposits are detected, treatment can be continued only if there is no progression of ARIA after careful observation of clinical symptoms and further MRI examination.

The drug price of aducanumab in the U.S. is assumed to be about $56,000 per year. It is unknown how many patients with Alzheimer's disease will actually receive the drug in the U.S., but it may depend on which insurance company they use, and whether or not their health insurance will cover the cost. The target population for aducanumab is likely to be patients with MCI or mild dementia with confirmed Aβ accumulation in the brain, which is estimated to be about 1 to 2 million people across the country.

Discussion of Aducanumab in Europe and Japan

Under these circumstances, in Europe, the European Medicines Agency decided on December 16, 2021, not to grant approval for aducanumab. Similarly, in Japan, the Pharmaceuticals and Medical Devices Agency decided not to approve the December 2020 application for approval of aducanumab for Alzheimer's disease, and that additional data are required for its approval.

Optimism in the Use of Lecanemab

Lecanemab (BAN2401) is a humanized IgG1 antibody from mouse monoclonal antibody mAb158 that selectively binds to soluble Aβ protofibrils [19]. In 2001, an APP mutation (Arctic mutation, APP E693G) was found in a Swedish patient with familial AD Aβ (Aβ1 - 42 Arc). In this mutation, the 22nd glutamate residue becomes a glycine residue, is truncated and is known to be highly aggregative and prone to forming protofibrils. Aβ protofibrils prepared from Aβ1-42Arc are used as antigens for producing monoclonal antibody, mAb158 (mouse antibody), which has strong binding ability to protofibrils prepared from unmutated Aβ as well as AβArc protofibrils, but binding ability to low molecular weight Aβ and the *N*-terminal sequence of Aβ (Aβ1-16) is over 200-fold weaker. In animal models of AD, mAB158 has been shown to selectively reduce Aβ protofibrils, thereby lowering Aβ levels and inhibiting Aβ deposition [20, 21]. Based on these preclinical data, a humanized IgG monoclonal antibody to mAB158 was created, BAN2401 and phase I (NCT02094729) and phase II (NCT01230853) clinical trials were conducted. Multiple phase III trials were launched.

The Clarity AD trial (NCT03887455) is a phase III trial to investigate the effect of lecanemab on mild cognitive impairment (MCI due to AD). It used a 10 mg/kg intravenous dose of lecanemab every two weeks and CDR-SB to determine change in clinical symptoms from baseline. The study was completed as scheduled in June 2022.

Meanwhile, the AHEAD3-45 trial (NCT04468659) was also designed for lecanemab (BAN2401). This was a trial for pre-AD patients at high risk of developing AD, including those with first-degree relatives who had dementia before age 75, those with apolipoprotein E4, or those with high levels of Aβ accumulation in the brain as determined by amyloid PET or CSF quantification levels by amyloid PET or CSF. Subjects received lecanemab 5 mg/kg intravenous infusion every 2 weeks for 8 weeks, followed by 10 mg/kg every 2 weeks for 96 weeks. The protocol was to receive an infusion of 10 mg/kg intravenously every 4 weeks for the following period up to 216 weeks, and long-term observation would be used to determine whether or not the infusion inhibits the onset of AD.

In September 2022, Eisai and Biogen announced positive topline results from Eisai's large global Phase 3 confirmatory clarity AD clinical trial of lecanemab, an investigational anti-Aβ protofibril antibody for the treatment of mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild AD (collectively known as early AD) with confirmed presence of amyloid pathology in the brain.

Clarity AD was a global confirmatory Phase 3 placebo-controlled, double-blind, parallel-group, randomized study of 1,795 people with early AD. The treatment group was administered a dosage of 10 mg/kg bi-weekly of lecanemab, with participants allocated in a 1:1 ratio to receive either placebo or lecanemab. The baseline characteristics of both placebo and lecanemab groups were similar and well balanced. Eligibility criteria allowed patients with a broad range of

comorbidities/comedications: hypertension, diabetes, heart disease, obesity, renal disease and anti-coagulants. Eisai's recruitment strategy for the clarity AD clinical trial ensured greater inclusion of ethnically and racially diverse populations in the U.S., resulting in about 25% of the total U.S. enrollment including Hispanic and African American persons living with early AD. Due to the inclusive eligibility criteria and the successful recruitment of diverse ethnic and racial populations in the U.S., Clarity AD's population is generally thought to be representative of the country's Medicare population.

Lecanemab treatment met the primary endpoint and reduced clinical decline on CDR-SB compared with placebo at 18 months in 27% of patients, which represents a treatment difference in the score change of -0.45 ($p = 0.00005$) in the analysis of intent-to-treat population (investors.biogen.com/static-files/5a31a1e3-4fbb-4165-921a-f0ccb1d64b65). Starting as early as six months, across all time points, the treatment showed highly statistically significant changes in CDR-SB from baseline compared with the placebo ($p < 0.01$). All key secondary endpoints were also met with highly statistically significant results compared with the placebo (all $p < 0.01$). Key secondary endpoints were the change from baseline at 18 months compared with placebo of treatment in amyloid levels in the brain measured by amyloid positron emission tomography (PET), the AD Assessment Scale-cognitive subscale 14 (ADAS-cog14), AD Composite Score (ADCOMS) and the AD Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL).

The incidence of amyloid-related imaging abnormalities-edema/effusion (ARIA-E), an adverse event associated with anti-amyloid antibodies, was 12.5% in the lecanemab group and 1.7% in the placebo group. The incidence of symptomatic ARIA-E was 2.8% in the lecanemab group and 0.0% in the placebo group. The ARIA-H (ARIA cerebral microhemorrhages, cerebral macrohemorrhages, and superficial siderosis) rates were 17.0% in the lecanemab group and 8.7% in the placebo group. The incidence of symptomatic ARIA-H was 0.7% in the lecanemab group and 0.2% in the placebo group. There was no imbalance in isolated ARIA-H (i.e., ARIA-H in patients who did not also have ARIA-E) between lecanemab (8.8%) and placebo (7.6%). The total incidence of ARIA (ARIA-E and/or ARIA-H) was 21.3% in the lecanemab group and 9.3% in the placebo group. Overall, the ARIA incidence profile of lecanemab was within expectations.

Lecanemab met the primary endpoint (CDR-SB) and all key secondary endpoints with highly statistically significant results. Eisai will discuss this data with regulatory authorities in the U.S., Japan and Europe with the aim to file for traditional approval in the U.S. and for marketing authorization applications in Japan and Europe by March 31, 2023.

Conclusion

A quarter of a century has passed since the introduction of donepezil in clinical use for patients with Alzheimer's disease. Since then, endeavor for development of better drugs for overcoming Alzheimer's disease has been continued without success until last year. In 2021, aducanumab was granted expedited approval by the FDA, the subject of controversy due to its poor Phase III results. The clinical use of aducanumab (Aduhelm) has been launched in U.S. under some restrictions.

The success of lecanemab in Phase III clinical trial in 2022 has brought further optimism for a leap forward in treatment of Alzheimer's disease. Although formal approval of lecanemab and other monoclonal antibody therapeutics is awaited, we can expect that an Alzheimer's disease drug with good efficacy might finally become available in the available near future.

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Conflicts of Interest

The author declares no potential conflicts of interest in writing this review.

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