REVIEW ARTICLE

Development of monoclonal antibody therapy against Alzheimer's disease

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Abstract

Understanding of the molecular pathology of Alzheimer's disease has been advanced, and amyloid β (Aβ) protein deposited in the core of amyloid plaques and phosphorylated tau protein constituting neurofibrillary tangles have been identified as the hallmark of Alzheimer's disease pathology. The development of disease-modifying drug has been focused on the amyloid cascade hypothesis, but neither the β-secretase inhibitors, γ-secretase inhibitors, nor γ-secretase modifiers have been successful. In 1999, administration of Aβ to transgenic mice as model animals for Alzheimer's disease was reported to significantly reduce amyloid deposition in the brain, which was the beginning of immunotherapy for Alzheimer's disease, but the antibody against amyloid (AN1792) clinical trial was discontinued due to the occurrence of aseptic meningoencephalitis in 2002. Recently, antibody therapy has been increasing year by year. Since the development of the first antibody therapeutic in 1986, 40 items in the oncology field and about the same number of monoclonal therapeutics in the non-cancer area have been approved as of 2020. In 2021, aducanumab has been approved by the FDA as an antibody therapeutic for early-stage Alzheimer's disease, albeit conditionally. In this paper, development status of monoclonal therapeutic agents for Alzheimer's disease will be reviewed, including aducanumab (Biogen), lecanemab (Biogen, Eisai), solanezumab (Eli Lily), crenezumab (Genentech), donanemab (Eli Lily), and gantenezumab (Hoffman-La Roche).

Key words: *Alzheimer's disease, immunotherapy, monoclonal antibody, disease-modifying drug, aducanumab*

INTRODUCTION

Alzheimer's disease is the most malignant disease in the 21st century due to the number of patients, the duration of illness, and the severity of the disorder. Researchers around the world have been making efforts to develop a disease-modifying drug for it. At present, there are 40 million people with dementia in the world and 6 million in Japan, 60-70% of which are due to Alzheimer's disease. The pathogenesis of Alzheimer's disease is closely related to aging of the brain, and the number of patients increases as the average life expectancy increases. Therefore, the number of patients with Alzheimer's disease will continue to double every 20 years, the number of patients worldwide is expected to reach 115 million by 2050.

In order to face with increasing number of dementia people, the United Kingdom has launched the National Dementia Strategy, and the United States, the National Alzheimer's Plan promoting national dementia countermeasures. Japan, which is the country aging at the fastest speed in the world, "Promotion Charter for Dementia Measures" was announced in June 2019, aimed at realizing a society in which people with dementia can continue to live in their own community in the best possible environment. The basic idea is "prevention and symbiosis", aiming for a society that delays the onset of dementia and allows people with dementia to spend their daily lives with hope, and emphasizes the perspectives of people with dementia and their families.

Cell biological research aimed at elucidating the pathophysiology of Alzheimer's disease and developing therapeutics has been vigorously pursued since the 1980s. The first drugs developed were cholinesterase inhibitors, such as donepezil (approved in the US in 1996 and Japan in 1999), galantamine, and rivastigmine, which aimed to suppress the degradation of acetylcholine, which is reduced in the brain of Alzheimer's disease. Subsequently, the NMDA antagonist memantine (Europe in 2002, US in 2003, Japan in 2011) was developed. Although these drugs temporarily improve cognitive function, the patient's

condition progresses and cognitive decline continues even if these drugs are administered, so they are not qualified to be the disease-modifying drugs of Alzheimer's disease. For more than 20 years, the development of disease-modifying drugs that can suppress the progression of Alzheimer's disease has been searched for without success.

Elucidation of the molecular pathology of Alzheimer's disease has been advanced, and amyloid β (Aβ) protein deposited in the core of amyloid plaque and phosphorylated tau protein constituting neurofibrillary tangles have been identified. Aβ is produced by the sequential action of β-secretase and γ-secretase from its precursor APP (amyloid precursor protein). The ratio of Aβ42 / Aβ40 is demonstrated to be elevated in the brain of familial Alzheimer's disease patients with APP, presenilin-1, and presenilin-2 mutations. All together with these findings, amyloid cascade hypothesis has become widely accepted as the basic pathology of Alzheimer's disease, and endeavor of disease-modifying agent development has been proceeded based upon the amyloid cascade hypothesis. However, none of β-secretase inhibitors, γ-secretase inhibitors, nor γ-secretase modifiers have yet come to the success.

DEVELOPMENT OF IMMUNOTHERAPY / ANTIBODY THERAPY

Recently, the number of biological drugs has increased. In particular, antibody therapy has been increasing year by year. Figure 1 shows the evolution of antibody therapeutics first approved by the European Regulatory Authority (EMA) and the US Food and Drug Administration (FDA) since 1986 (Kaplon, 2020). After the first antibody therapeutics in 1986, the number of antibody therapeutics has been gradually increasing, but initially most of them were antibody therapeutics targeting cancer. The number has increased rapidly since 2015, about 40 items in the oncology area and about 80 items in the non-cancer area have been approved as of 2020. The number of antibody therapeutic agents for diseases other than the oncology area is increasing after 2015 (Figure 2). (Kaplon, 2021)

Antibody therapies approved outside the oncology area in 2020 are as follows; (the trademark, target molecule, and target disease are shown in parentheses after the antibody name). Teprotumumab (Tepezza, IGF-1, Thyroid eye disease), Eptinezumab (Vyepti, CGRP, migraine prevention), Inebilizumab (Uplizna, CD19, Neuromyelitis optica), Satralizumab (ENSPRYNG, IL-6R, Neuromyelitis optica), Atoltivimab, maftivimab, odesivimab (Inmazeb, Ebola virus, Ebola virus infection) There were 6 items (GD2, Neuroblastoma).

Antibody drugs under review outside the oncology area in 2020 are shown in parentheses along with the target molecule and target disease. Tanezumab (NGF, Osteoarthritis pain), Narsoplimab (MASP-2, hematopoietic stem cell transplant-associated thrombotic microangiopathy), Evinacumab (Angioprotein-like pro-

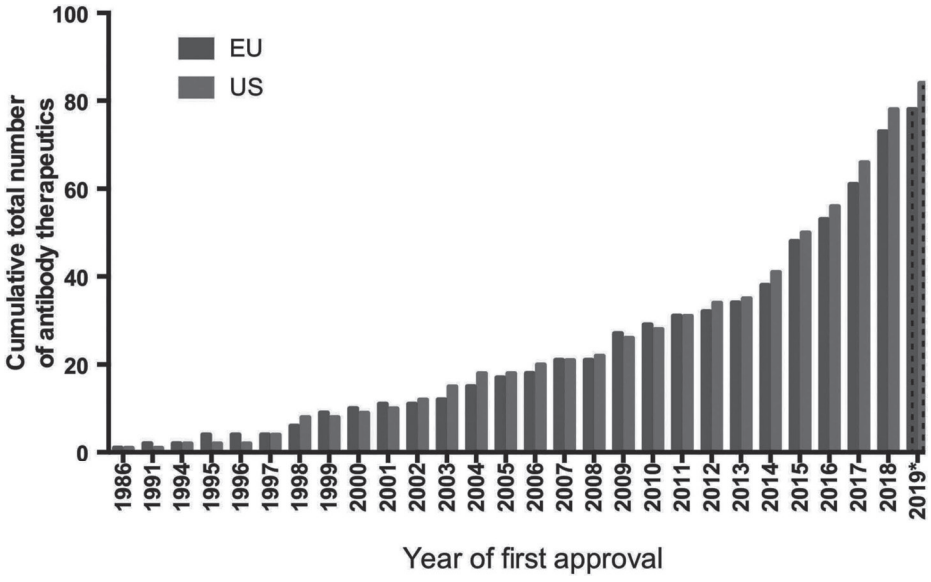

Figure 1. Number of antibody products approved in US or Europe 1986-2019.
Kaplon H, Muralidharan M, et al. Antibodies to watch in 2020. mAbs, 12(1), 1703531, 2020

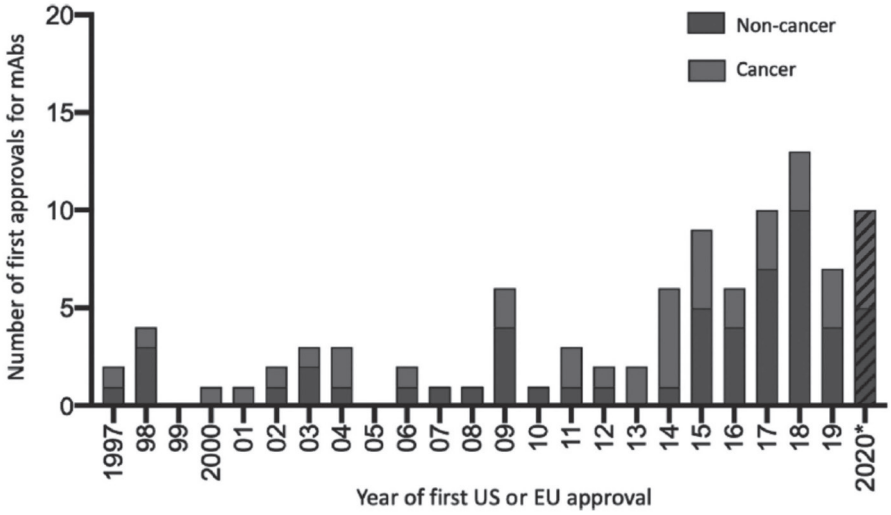

Figure 2. Antibodies reviewed for the first time in US or Europe 1997-2020.
Kaplon H, Muralidharan M, et al. Antibodies to watch in 2020. mAbs, 12(1), 1703531, 2020

tein 3, Hypercholesteromia), 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 (Ebora virus, Ebola virus infection), Bimekizumab (IL-17A and IL-17F, Psoriasis), There are 10 items, Aniflolumab (IFNa, b, ω receptor 1, Systemic lupus erythematosus) and Sutimlimab (C1s, Cold Agglutinin disease). It was noteworthy that aducanumab was the first to be reviewed on this list as an antibody treatment for early-stage Alzheimer's disease.

BEGINNING OF AMYLOID β (Aβ) IMMUNOTHERAPY

In 1999, Shenk (Elan) reported that administration of Aβ to transgenic mice used as model animals for Alzheimer's disease reduced amyloid deposition (Shenk, 1999), which gave a large impact because the intracerebral immune system was thought independent of peripheral immune system. Shenk et al. reported that Aβ-immunized mice at an early age suppressed plaque formation, neurite retraction, and astroglial proliferation, and aged mice showed significant suppression of progression of pathological changes such as intracerebral amyloid deposition. Amyloid plaques in the brain were also reduced or eliminated (Shenk, 1999). It was also reported that Aβ vaccine therapy for mice with high expression of APP was effective in suppressing the decline in learning and memory due to aging (Janus, 2000; Morgan, 2000).

Based on the results of these animal experiments, Elan conducted a clinical trial of the vaccine AN1792 consisting of Aβ1-42 and an adjuvant (QS-21). A phase I trial of the AN1792 vaccine was conducted in 2000 in patients with mild to moderate Alzheimer's disease in the United States and the United Kingdom without serious side effects. Subsequently, in 2001, a phase II study was conducted in the United States and Europe in patients with mild to moderate Alzheimer's disease. In this phase II trial, aseptic meningoencephalitis occurred in 6% (18/300) of patients who received the vaccine, forcing the AN1792 trial to be discontinued in 2002. Although the trial was interrupted with only 1-3 vaccinations, but some challenges and useful information were obtained.

The biggest problem was the development of meningoencephalitis, and it was necessary to consider how to develop a vaccine without such side effects. Regarding the pathogenic mechanism of meningoencephalitis due to vaccination, it is considered to be based on the activation of Th1 type CD4 positive cells that respond to Aβ. It is preferable to use an Aβ sequence that activates B cells (Th2 reaction) to produce an antibody with less activation of T cells involved in the cell-mediated immunity. It is known that Th1-type T cell activation is likely to be induced on the C-terminal side of Aβ, and Th2 reaction is likely to be induced on the N-terminal side. In subsequent immunotherapy, the N-terminal partial sequence of Aβ is used for the development of vaccines.

As for useful information, about 20% of patients who received AN1792 showed serum IgG antibody titers against Aβ up to 2,200-fold. In the reacted group, a tendency to decrease tau in cerebrospinal fluid was

also observed. Although no significant improvement effect was observed in various cognitive function tests, a general function analysis (Neuropsychological Test Battery (NTB)) showed significant improvement. In an autopsy case of a person who died in an accident after receiving AN1792, the amyloid plaque in the brain had been removed, microglia had accumulated at the site where the amyloid plaque disappeared, and T cells were found around the blood vessels of the meninges (Nicoll, 2003).

TYPES AND MECHANISMS OF AMYLOID β SEQUESTRATION BY IMMUNOTHERAPY

Immunotherapy is classified into two types: vaccine therapy in which an antigen is administered (active immunization), and antibody therapy in which an antibody is administered (passive immunization). The difference between vaccine therapy and antibody therapy is that antibody therapy is less likely to cause meningoencephalitis, which is a major concern with vaccines, and that antibody therapy can be expected to be effective even for non-responders who are less likely to produce antibodies with vaccines. However, from the viewpoint of manufacturing cost, vaccines generally have an advantage that they can be supplied at low cost.

Most of the vaccine therapies being investigated use the N-terminal sequence of Aβ aimed at avoiding meningoencephalitis observed in the AN1792 clinical trial while retaining the ability to produce anti-Aβ antibody. Aβ1-7 is used for ACC-001 of Elan / Weiss, which is in the most advanced stage, and Aβ1-6 sequence is used for CAD-106 of Novartis.

As for antibody therapy, various antibodies have been examined by many research groups. Regarding epitopes, antibodies that recognize the N-terminal sequence, intermediate part sequence, and C-terminal part were developed. Elan / Weiss's bapinuzumab (AAB-001) uses the N-terminal sequence of Aβ, Eli Lilly's solanezumab (LY2062430) uses the intermediate sequence of Aβ, and Pfizer's PF-04360365 uses the C-terminal of Aβ as the epitope.

Three hypotheses have been considered regarding the mechanism of action of Aβ antibodies (Monsonego, 2003). First, antibodies permeate the blood brain barrier (BBB) from the blood, migrate into the brain, bind to amyloid aggregates in the brain, and then phagocytose microglia in the brain via Fc receptors. Elan/ Weiss's Bapinuzumab etc. have been developed with this idea. The second is that the antibody permeates the BBB from the blood and migrates into the brain to dissolve Aβ from the amyloid aggregates in the brain and suppress further aggregation. The third hypothesis is that antibodies extract and transfer Aβ in the brain from the blood without penetrating BBB into the blood, and Eli Lilly's solanezumab has been developed based on this idea. (Figure 3)

AMYLOID β ANTIBODY THERAPY

The firstly developed antibody against Alzheimer's disease were bapinuzumab (Elan / Weiss) and solanezumab (Eli Lilly). In a phase II study of bapinuzumab, 234 patients with mild to moderate Alzheimer's were given 4 doses of bapinuzumab (0.15, 0.5, 1.0, and 2.0

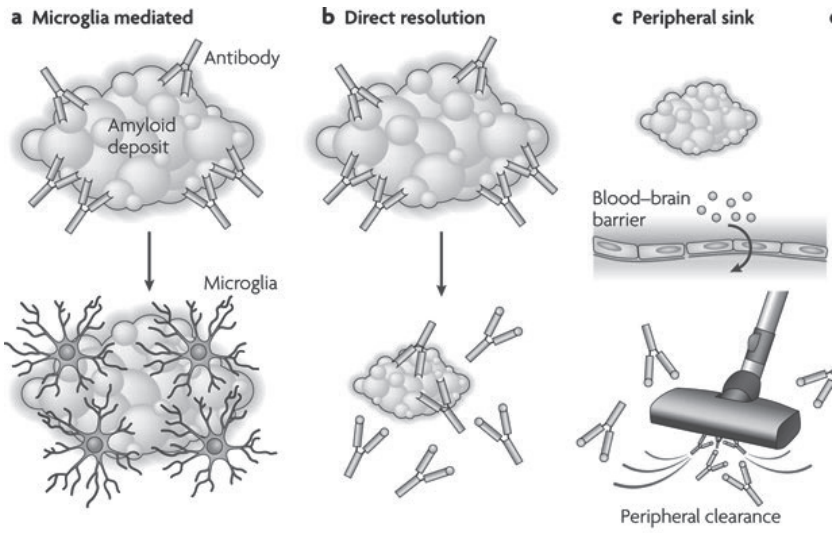

Figure 3. Hypothetical mechanism of amyloid clearance from the brain.

mg/ kg) intravenously 6 times every 13 weeks within a period of 18 months. MRI showed angiogenic edema in 12 patients who received bapinuzumab as an adverse event (1, 3, and 8 cases in the 0.15, 1.0, and 2.0 mg /kg dose, respectively), of which 10 had the apolipoprotein E4 allele. Endpoint evaluation was assessed by ADAS-cog, NTB, DAD, CDRSB, MMES. CSF tau and MRI brain volume measurements were analyzed separately for ApoE4 carriers and non-carriers. In terms of efficacy, ADAS-cog and NTB tended to be effective in all populations. In addition, the efficacy was higher in non-carriers than in ApoE4 carriers, as statistically significant and clinically significant effects were observed at multiple endpoints. The results showed that the non-ApoE4 carrier group also had an inhibitory effect on the decrease in brain volume. Based on the results of this Phase II clinical trial, Phase III clinical trials were conducted at different doses for ApoE4 carriers and non-carriers, but the results were not satisfactory and development was discontinued.

Many antibody therapy followed bapinuzumab trials, including solanezumab. More than two decades since 1992, all drug discovery for Alzheimer's disease has continued to fail in PIII clinical trials, and the pessimism for drug discovery of Alzheimer's disease-modifying drug spread among researchers and academia.

Although the molecular pathology has been elucidated to some extent, and many drug candidates have been developed based on such pathological hypothesis, with confirmed effectiveness up to preclinical development, none of them have been found effective and useful in clinical trials. There was intense debate on how to understand the discrepancy between animal study and human clinical trials. In such discussions, several speculations were discussed; (1) the amyloid cascade hypothesis may not be correct, (2) amyloid removal may not necessarily lead to improvement of clinical symptoms, and (3) the method of human clinical trials may not be correct. Out of these discussions, the framework of clinical trials for the development of disease-modifying drugs for Alzheimer's disease has been changed significantly.

Regarding how to proceed with clinical trials, a new framework has been adopted. In previous clinical trials, the framework was to examine the effect on patients who developed Alzheimer's disease symptoms by evaluation of improvement of cognitive function and other symptoms, which is relatively difficult to show significant difference by intervention. Under the new framework of clinical trials, pre-symptomatic or pre-clinical subjects are recruited using biomarkers. and a new clinical trial was designed with the framework to investigate the effect of drugs that suppress the transition from high-risk patients to the onset of dementia.

The new clinical trial frameworks require the collection of detailed data such as amyloid PET, genetic testing, biomarker quantification, and cognitive function assessment to correctly select high-risk individuals, from several hundreds of people. A high-risk population, and a long observation period of at least 3-4 years is required, which naturally costs huge expense. Several antibody drugs being investigated under such platforms are listed in Table 1 as of 2020.

Table 1. Monoclonal antibodies against Amyloid beta on clinical stage as of year 2021

Table 1 Properties of selected anti-Aβ antibodies currently tested in clinical trials for AD

mAb clinical candidate	Mouse antibody analog	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 Eisai Co.
Solanezumab	M266	Phase III, recruiting	M>>A	16-26	Eli Lilly and Co.
Crenezumab (MABT5102A)	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	gantenerumab	Phase III, recruiting	A>M	3–11,18–27	Hoffman-La Roche Inc.

Decourt B, Boumelhem F, et al. Critical appraisal of amyloid lowering agents in AD. Current Neurology and Neuroscience Reports, 21, 39, 2021

ADUCANUMAB

Aducanumab is a recombinant human IgG1 antibody produced by Neurimmune, which was picked up from a library of peripheral blood lymphocytes collected from elderly people with normal cognitive function. It was sold to Biogen in 2007 to develop into monoclonal antibody therapy against Alzheimer's disease. It binds to soluble and insoluble Aβ, but has more than 10,000-fold selectivity for Aβ polymers. It has the Aβ3–7 region as an epitope and is thought to selectively bind to oligomers and fibrils (Arndt, 2018).

Preclinical administration of aducanumab to transgenic model animals of Alzheimer's disease (Tg2576) reduced Aβ plaque in the brain of young 9-month-aged animals in a dose-dependent manner, but decrease in Aβ was not observed in 22-month-old animals. It was considered that aducanumab inhibits the polymerization of Aβ rather than the removal of existing Aβ. Aβ reduction in animal experiments did not lead to improvement in cognitive function.

In 2016, a P1a clinical trial (NCT01397539) was conducted on 53 patients with Alzheimer's disease. No adverse side effects were observed with low dose ≤ 30 mg/ kg aducanumab, but amyloid-related imaging abnormalities (ARIA) were observed with high dose 60 mg/ kg aducanumab. Interestingly, plasma Aβ40 and Aβ42 were elevated over 3 weeks in patients receiving aducanumab 60 mg / kg, suggesting that high doses of aducanumab were bound to soluble Aβ monomers to withdraw from the brain to serum (Ferrero, 2016). However, there was no significant difference in cognitive function 24 weeks after administration in the 13-item Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog13).

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

With these results, two large-scale PIII clinical trials "ENGAGE" (NCT02477800) and "EMERGE" (NCT02484547) were conducted. Both trials were conducted for mild cognitive impairment (MCI) and mild dementia due to Alzheimer's disease, and CDR-SOB was set as the primary endpoint. The original plan was to apply for approval in 2020.

In March 2019, Biogen announced the discontinuation of the clinical trial because it was unlikely that any improvement in the primary endpoint would be observed in the ENGAGE clinical trial, although there was a promising trend in the EMERGE clinical trial based on the results of the interim evaluation (Biogen, 2019a). This interim analysis was the result of analysis using data from 1748 patients who completed 18 months of clinical trials by the end of 2018, but it was judged that it would be difficult to achieve the primary endpoint in any of the clinical trials.

However, in October 2019, Biogen analyzed data from 3285 controls and found that high-dose aducanumab (100 mg / kg) was useful in both trials, and Biogen announced to apply for the FDA's review. In the EMERGE trial, the CDR-SOB score at week 78 showed a significant improvement in the high-dose group compared to the placebo group (22% vs. placebo, p = .01), as well as in the MMSE. (18% vs. placebo, p = .06), ADAS-cog (27% vs placebo, p = 0.01), AD-ADL (40% vs. placebo, p = 0.001). A reanalysis of discontinued trial data revealed that the initial dose was too low, arguing that the EMERGE trial had shown clinical utility (Biogen, 2019b). The announcement concluded that high-dose aducanumab administration caused a statistically significant effect on the suppression of symptom progression in patients with early-stage Alzheimer's disease (Biogen, 2019a). Biogen applied to the FDA for approval of aducanumab. However, there were some opinions against this application.

The results of the aducanumab analysis were submitted to the FDA Expert Committee on November 6, 2020, but many expert advisors commented that the results were inadequate. The discussions by the expert committee were summarized in the following four issues. (1) Can the 302 clinical trial (EMERGE) be considered as sufficient evidence that aducanumab is effective as a treatment for Alzheimer's disease when viewed independently of the 301 clinical trial (ENGAGE)? (voting results: 1 in favor, 8 against, 2 pending) (2) Is the 103 clinical trial (PRIME) the basis for supporting the therapeutic efficacy of aducanumab? (voting results: 0 in favor, 7 against, 4 pending) (3) Is it possible to provide sufficient evidence for the efficacy of aducanumab in terms of pharmacodynamics for the pathophysiology of Alzheimer's disease? (voting results: 5 in favor, 0 against, 6 pending) (4) When the results of exploratory analysis of clinical trials 301 and 302 and the pharmacodynamic effects of clinical trials 103 and Alzheimer's disease on the pathophysiology are considered, the results of clinical trial 302

show the effectiveness of aducanumab as a therapeutic agent for Alzheimer's disease? (voting result: 0 for, 10 against, 1 pending)

As can be seen in this summary, most experts disagreed with the approval of aducanumab. This is because the content is different from the previous announcement, and the clinical trial was incompatible with the principle of judging the effect based on predetermined evaluation items.

A hearing was held on December 5, 2020 for aducanumab. The British Alzheimer's Disease Association has questioned the usefulness of aducanumab, but the American Alzheimer's Disease Association has urged the FDA to approve it.

After this hearing, the FDA was to reach a conclusion by March 2021, but resubmission of materials was required and the decision was postponed until June 8, 2021. The FDA has announced the conclusion of accelerated approval for aducanumab. The FDA has made decisions in the past that differ from the views of the expert committee, but it goes without saying that this is an unusual decision.

The FDA decided to approve it quickly, but there were many doubts about this decision. For example, Knopman et al. said that retrofit analysis results are often inaccurate and require additional data for FDA approval, requiring an additional trial of high-dose aducanumab for at least 78 weeks (Knopman, 2020). Eleven experts reportedly served on the FDA's Peripheral and Central Nervous System Drugs Advisory Committee, which reviewed aducanumab by June 13, 2021. Three of them have resigned following the decision to expedite approval. Ripples are widespread, with one of them saying, "This accelerated approval is probably the worst decision in recent US drug approvals."

Many experts point out that aducanumab was approved based on the alternative endpoint (surrogate endpoint) of "reduce in amyloid β (Aβ)" without sufficient evidence of its clinical usefulness of "suppressing cognitive decline," which is the most important for patients and their families. At this time, there is no clear evidence that a decrease in Aβ will reduce the decline in cognitive function.

This time, the FDA's accelerated approval is a conditional approval. Accelerated approval is a mechanism for approving a drug based on alternative endpoints that can predict its clinical usefulness for serious or life-threatening diseases. With regard to aducanumab, it was concluded that rapid approval was based on the results of dose- and time-dependent reductions in intracerebral Aβ deposition assessed by amyloid PET in two Phase III clinical trials. However, reduction of amyloid β in the brain is only an alternative endpoint, not a clinical endpoint of suppressing cognitive decline. In expedited approval of aducanumab, the FDA explained that a reduction in amyloid β would bring clinical benefit to patients, but would impose a confirmatory trial as an approval requirement to confirm its clinical utility. If the confirmatory trial does not show clinical utility by February 2030, the approval will be revoked.

LECANEMAB

Lecanemab (BAN2401) is an IgG1 antibody that is a humanized mouse monoclonal antibody mAb158 that selectively binds to soluble Aβ protofibrils (Logovinsky, 2016). In 2001, the APP mutation (Arctic mutation: APP E693G) found in familial AD patients in Sweden resulted in the excision of Aβ (Aβ1-42 Arc) in which the 22nd glutamate residue is a glycine residue. It is known that it has high cohesiveness and easily forms protofibrils. Amyloid gradually aggregates from a monomer to a polymer with the formation of a β-sheet structure, and the neuronal cytotoxicity of Aβ is a soluble aggregate. Among Aβ aggregates, those with a relatively small molecular weight are oligomers (called Aβ* , Amyloid β-derived diffusible ligands: ADDL, Globulomers, Spheroids, and others), and high molecular weight soluble aggregates are called protofibrils (PF). Anti-Aβ protofibril antibody mAb158 (mouse antibody) prepared using Aβ protofibril prepared from Aβ1-42 Arc as an antigen has strong binding ability to protofibril prepared from unchanged Aβ as well as Aβ Arc protofibril. However, it has a binding ability of 200 times or more weaker to the N-terminal sequence of low molecular weight Aβ and Aβ (Aβ1-16), and no binding ability to the C-terminal sequence of Aβ (Aβ17-40). In AD model animal experiments, mAB158 has been shown to reduce Aβ levels and suppress Aβ deposition by selectively reducing Aβ protofibrils (Söllvander, 2018; Tucker, 2015). Based on such preclinical data, a humanized mAB158 IgG monoclonal antibody was generated (BAN2401) and was conducted in Phase I (NCT02094729) and Phase II (NCT01230853) clinical trials. Several phase III clinical trials are being conducted.

Clarity AD trial (NCT03887455) was a phase III trial investigating the effect of lecanemab on mild cognitive impairment (MCI due to AD), in which lecanemab 10 mg/ kg was injected every two weeks and CDR-SOB score will be compared with baseline score. This is a clinical trial to compare the effect of suppressing

the transition of clinical symptoms with placebo, which is scheduled to be completed in June 2022.

AHEAD3-45 clinical trial (NCT04468659) is also being conducted for leacanemab (BAN2401). This trial is for presymptomatic AD at high risk of developing AD, with first-degree relatives having a family member who developed dementia before age 75, those with the apolitical protein E4, or amyloid PET positive or low CSF amyloid. The target is people with high levels of Aβ accumulation in the brain. Subjects received a lecanemab 5 mg / kg infusion for 8 weeks once every 2 weeks, followed by a biweekly 10 mg / kg infusion for 96 weeks, followed by 10 mg / kg every 4 weeks. It is a protocol to continue intravenous drip infusion until 216 weeks, and it will be examined whether to suppress the onset of AD by long-term observation.

SOLANEZUMAB

Solanezumab is a monoclonal antibody that uses the central part of Aβ as an epitope, which has been shown to promote clearance of Aβ in the brain in animal experiments (DeMattos, 2001; Legleiter, 2004). Solanezumab has been shown to reduce Aβ levels in CSF by binding to Aβ in serum and withdrawing Aβ in the brain (DeMattos, 2002). Four clinical trials have been conducted so far. Expedition 1 (NCT00905372) and Expedition 2 (NCT00904683) have already been completed, followed by Expedition 3 (NCT01900665) and Expedition PRO (NCT02760602). Both trials were conducted to investigate whether solanezumab could suppress cognitive decline in MCI and suppress its progression to AD (Doody, 2014).

Specifically, in the Expedition 3 clinical trial for patients with mild AD, it was examined whether cognitive decline could be suppressed, but the result was negative (Honig, 2018). Furthermore, the Expedition PRO clinical trial, which investigated whether to suppress the onset of AD in high-risk presymptomatic subjects, could not show its usefulness. The usefulness of solanezumab has been investigated even after the completion of the Expedition study, and the ongoing clinical trial of solanezumab is the DIAN-TU clinical trial.

The DIAN-TU clinical trial (NCT01760005) is a phase II / III clinical trial in subjects with a genetic background of PS1 mutation, and it is examined whether it suppresses the rate of cognitive decline and suppresses changes in biomarkers.

In a parallel administration study of solanezumab and gantenerumab, solanezumab was compared with gantenerumab at increased doses every 4 weeks. Gantenerumab is a humanized IgG1 antibody against Aβ in the brain and has been known to reduce Aβ in AD transgenic animals (Klein, 2021) and humans (Klein, 2019). The effects of solanezumab were shown in the four cognitive function evaluation tests used in the DIAN study (Wechsler Memory Scale-Revised Logical Memory Delayed Recall Test, Wechsler Adult Intelligence Sale Digit Symbol Substitution Test (WAIS), International Shopping List Task (ISLT), and MMSE). The DIAN-TU study is expected to involve 490 people and will end in July 2022.

CRENEZUMAB

Crenezumab (MABT5102A) is a humanized anti-Aβ monoclonal IgG4 antibody that binds to many Aβ species, which is particularly selective for pentamers and hexamers among Aβ polymers (Zhao, 2017). Crenezumab binds to both Aβ monomers and polymers, and in addition, crenezumab has a polymerization inhibitory effect, which is expected to dissolve Aβ polymers and protect nerve cells from the neurotoxicity of oligomers (Ultsch,2016). Crenezumab was created under the hypothesis that the constant region of human IgG4 can modify Fc effector function and reduce vascular side effects (Adolfsson, 2012). In a preclinical study of Tg2576 mice, intracerebral administration of crenazumab did not provoke an inflammatory response (Ultsch, 2016). Phase Ib clinical trial (GN29632) confirmed tolerability of crenezumab ≤ 120 mg / kg IV every 4 weeks (Guthrie, 2020) (NCT02353598), and multiple Phase II clinical trials in patients with mild to moderate Alzheimer's disease was conducted.

The primary endpoint of the ABBY clinical trial (NCT01343966) was the ADAS-Cog12 and CDR-SOB scores at 73 weeks compared to the baseline (Cummings, 2018). The primary endpoint of the BLAZE trial (NCT01397578) was PET-induced reduction in amyloid levels in the brain. Secondary endpoints were CSF biomarker levels at week 69 compared to baseline and glucose metabolism by PET at week 73. ADAS-Cog12 and CDR-SOB were configured (Salloway, 2018). The results of both trials were negative and neither the primary nor secondary endpoints showed efficacy.

However, subsequent analysis suggests that early treatment with crenezumab may be possible in patients with very mild illness in the high-dose crenezumab group, and the effect of high-dose crenezumab effect is supported by the finding from PIb (GN29632). Based on these results, two high-dose

crenezumab phase III clinical trials were conducted. In the CREAD (NCT02670083) and CREAD2 trials (NCT03114657), 60 mg/ kg, four times the amount of crenazumab used in the phase II trial, was administered, assessing changes in CDR-SOB after 105 weeks (Bittner, 2020). It was interrupted by an analysis in the middle of the trial (Yoshida, 2020). A phase II clinical trial (NCT01998841) is ongoing for presymptomatic subjects with the E280A mutation in PSEN1 for crenazumab, scheduled to be completed in February 2022.

DONANEMAB

Donanemab (LY3002813 or N3pG) is a recently developed humanized IgG1 anti-Aβ monoclonal antibody that uses Aβ (p3-42) with an N-terminal pyroglutamate as an epitope (Irizarry, 2016). Although studies are underway in patients with MCI and AD, donanemab has been shown to be safe and tolerable in multiple-dose escalating clinical trials. Subjects were assigned 0.1 to 10 mg / kg donanemab or placebo and were observed for 12 weeks, with a 40–50% reduction in Aβ in the 10-mg/ kg group. The TRAILBLAZER-ALZ trial also suggests the usefulness of donanemab in early-stage AD patients (Mintun, 2021). This multicenter, randomized, double-blind, placebo-controlled phase II trial examined the effect of donanemab on cognitive function in patients with early prodromal AD. Patients received 700 mg donanemab (˜10 mg/ kg) or placebo infusion for 72 weeks followed by 1400 mg (˜ 20 mg/ kg) every 4 weeks. The primary endpoint of the TRAILBLAZER-ALZ trial is the change in iADRS from baseline after 76 weeks, and the secondary endpoints are CDR-SOB, ADAS-Cog13, MMSE, Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS- iADL) together with Aβ amount and tau amount. At week 76, the donanemab group showed a significant improvement on the Integrated Alzheimer's Disease Rating Scale (iADRS) compared to the placebo group. The donanemab group did not show a significant improvement in most of the secondary endpoints, but florbetapir PET and tau PET showed a significant decrease in Aβ and tau. It has been suggested that such improvements shown in early AD patients may also be seen in more advanced AD patients. In addition to the TRAILBLAZER-ALZ trial, Eli Lilly has added donanemab to the symptoms of early AD patients. A phase II clinical trial (NCT04437511), has been started to investigate its usefulness. In this TRAIL BLAZER-ALZ2 clinical trial, the change in CDR-SOB from baseline is evaluated and the subjects are those who show memory deterioration continuing for 6 months or more by the patient and the caregiver. The result is expected by 2024. Donanemab has been shown to improve cognitive function as well as to decrease Aβ in the brain, which might be a promising immunotherapy.

GANTENERUMAB

Gantenerumab is a humanized IgG1 antibody to remove Aβ in the brain by activating cellular factors which bind to polymerized Aβ(Bohrmann, 2012). A recent report by Klein et al. found that subcutaneous administration of 1200 mg of gantenerumab antibody every 4 weeks reduced Aβ in presymptomatic to moderate AD patients. This open trial was performed with the aim of reducing Aβ levels in the brain by PET from baseline at 52 weeks and 104 weeks. In a 2021 report, Klein et al. reported that subcutaneous administration of 1200 mg of gantenerumab reduced brain Aβ levels 36 months after administration (Klein, 2021). As mentioned earlier, gantenerumab is undergoing the DIAN-TU Phase II clinical trial (NCT01760005). A multicenter, open-label, single-arm, pharmacodynamic Phase II clinical trial in early AD patients (NCT04592341) is scheduled to end in February 2024. The primary endpoint of this trial was amyloid PET to reduce Aβ from baseline after 104 weeks, A randomized, double-blind, placebo-controlled, parallel-group Gantenerumab phase III trial in early AD patients has also begun (NCT03444870) and is scheduled to end in November 2023. The primary endpoint of this trial is CDR-SOB compared to baseline after 116 weeks.

INTRODUCTION OF MONOCLONAL ANTIBODY THERAPEUTIC AGENTS TO JAPAN

The price of aducanumab in the United States is expected to be around $ 56,000 per year, which will be 6 million in Japanese yen. It is unknown how much Alzheimer's disease patients will actually use it in the United States, but it may vary depending on the insurance company. The target of aducanumab is thought to be patients with MCI and mild dementia who have been confirmed to have amyloid β accumulation in the brain, which is estimated to be about 1 to 2 million people in the United States. It is unknown how many of them will be treated by aducanumab.

In December 2020, Biogen filed an application for approval of aducanumab for Alzheimer's disease in

Japan. Considering that the examination period for ordinary medicines is about one year, it is expected that a conclusion will be reached within 2021.

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