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Review

Anti-amyloid-β Antibodies and Anti-tau Therapies for Alzheimer's Disease: Recent Advances and Perspectives

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Amyloid-β (Aβ) plaques and neurofibrillary tangles containing phosphorylated tau protein are major hallmarks of Alzheimer's disease (AD). Drug discovery efforts to target Aβ and tau have been the primary focus for several decades. Recently, substantial breakthroughs have been achieved in the clinical development of Aβ antibodies; aducanumab was approved under conditional accelerated pathway by Food and Drug Administration (FDA) in the U.S. as the first disease-modifying agent for treating AD, and lecanemab has been granted traditional full approved in the U.S. and Japan. In addition, donanemab met the primary endpoint in a phase 3 study. On the other hand, tau-targeting therapies have failed to show clinical benefit although that increased tau levels show a strong correlation with cognitive impairment relative to Aβ depositions. Currently, tau immunotherapies, such as anti-tau antibodies and tau vaccines, have shown functional benefits in clinical trials. Also, clinical trials for combination therapy of Aβ and tau antibodies to see their potential are being investigated. In this review, we provide updates on the results of clinical trials of anti-Aβ antibodies and anti-tau therapeutics and suggest future directions for these therapeutics.

Key words Alzheimer's disease, amyloid-β, tau, antibody

1. Introduction

Alzheimer's disease (AD), the most common case of dementia, accounting for 50–70% of cases, is a progressive neurodegenerative disease characterized by decline of cognition and memory. The number of people living with dementia worldwide was estimated to be 55 million in 2019, and the numbers are expected to reach 139 million in 2050, with two-thirds of those affected living in low- and middle-income countries. The economic costs associated with dementia are formidable and are estimated to more than double from 1.3 trillion dollars per year in 2019 to 2.8 trillion dollars in 2030.[1] Amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) containing phosphorylated tau protein are the hallmarks of AD. Research on longitudinal biomarkers has shown that Aβ accumulation starts decades before the onset of clinical symptoms followed by the spread of NFTs, which then causes neuronal and synaptic loss leading to cognitive impairment.[2] Numerous accounts of preclinical and clinical evidence suggest that the Aβ cascade and the hyperphosphorylation of tau play major roles in AD pathogenesis.[3] Therefore, targeting Aβ or tau have been the primary focuses for several decades *via* multiple approaches.[4,5] In Aβ-targeted approaches, substantial breakthroughs have been made with Aβ antibodies. Indeed, aducanumab was approved under conditional accelerated pathway by Food and Drug Administration (FDA) in the U.S. as the first disease-modifying agent for treating AD,[6] and lecanemab have been granted traditional full approval in the U.S. and Japan.[7,8] In addition, donanemab was reported to meet the primary endpoint in a phase 3 study, providing clinical benefits for some clinical scales and biomarkers, such as Aβ plaques and tau, which should accelerate the path to its approval.[9] Regarding tau, although clinical studies of many candidates had to be discontinued due to lack of efficacy or toxicity, recent progress in tau-targeting therapies is evident but without successful translation into clinical benefits. The aim of this review is to highlight recent advances and perspectives on anti-Aβ antibodies and anti-tau therapeutics.

2. Anti-Aβ Antibodies

2.1. The Amyloid Oligomer Hypothesis In 1992, based on the finding of a pathogenic mutation in the Aβ precursor protein (APP) gene from familial Alzheimer's disease patients, Hardy and Higgins formulated the amyloid hypothesis that brain Aβ plaque deposition could be the main pathogenic factor of AD.[10] The Aβ formation begins with APP cleavage by β-site amyloid precursor protein cleaving enzyme 1 (BACE1)

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to generate a soluble extracellular fragment (sAPPβ) and a cell-membrane-bound fragment (C99). Next, C99 is cleaved intracellularly by γ-secretase, yielding an amyloid intracellular domain and Aβ peptides of variable lengths[11] (Fig. 1). Of these Aβ peptides, Aβ42 having 42 amino acids is thought to be crucial for AD pathology, as it is more toxic and aggregates more easily than other forms. Aβ monomers aggregate to form various species, such as oligomers, consisting of soluble low molecular weight oligomers, protofibrils, and insoluble fibrils, ultimately forming Aβ plaques (Fig. 2). Although Aβ plaques were believed to be the pathogenic form of Aβ, a growing amount of pharmacological evidence suggests that Aβ oligomers, especially soluble low molecular weight oligomers and protofibrils, are the most likely pathogenic form of AD.[12] In particular, severity of cognitive dysfunction in AD patients was found to correlate better with the level of soluble Aβ species than insoluble Aβ species in the brains.[13,14] In addition, the selective toxicity of Aβ oligomers observed in cellular assays further supported the oligomer hypothesis. Several mechanisms, such as direct neurotoxicity *via* ion channel pore formation or receptor binding to activate signaling pathways, are considered to induce neuronal loss and cognitive decline by Aβ oligomers.[15] Finally, recent advances achieved by the three monoclonal antibodies of aducanumab, lecanemab and donanemab offer support for the amyloid cascade being a pathogenesis pathway to AD. We provide updates on the research and development of these three antibodies.

2.2. Aducanumab Aducanumab was originally discovered by scientists at Neurimmune and then licensed to Biogen and Eisai for clinical development. It is a recombinant human antibody derived from a blood lymphocyte library collected from healthy elderly donors without signs of cognitive impairment. Importantly, the immune system of the donors successfully resisted AD, and therefore the antibody from their blood samples could serve as potential therapeutics through a reverse translational medical approach.[16] Binding kinetics and affinity measurement studies confirmed that aducanumab selectively targeted Aβ oligomers.[17]

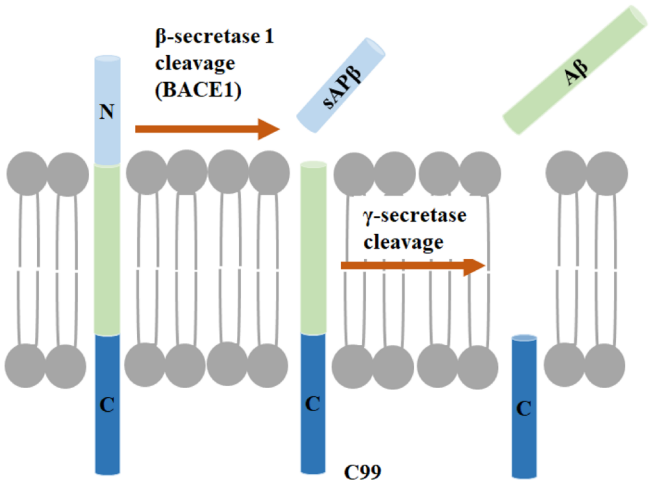

Fig. 1. The Process of Aβ Formation

Two phase 3 studies (EMERGE and ENGAGE) of aducanumab showed discrepancy regarding efficacy of slowing cognitive decline.[18] While EMERGE met the primary endpoint of the Clinical Dementia Rating-Sum of Boxes (CDR-SB), where the highest dose (10 mg/kg, every 4 weeks) of aducanumab led to significant reduction in the CDR-SB score by about 20% in patients with early AD (mild cognitive impairment (MCI) due to AD and mild AD dementia) at 78 weeks, ENGAGE did not meet the primary endpoint. However, aducanumab consistently showed significant Aβ plaque clearance in the brain (amyloid Positron Emission Tomography (PET): about 70% decrease in EMERGE and about 59% decrease in ENGAGE) and phosphorylated tau reduction in the plasma (surrogate biomarker of NFTs in the brain: about 13% decrease in EMERGE and about 16% decrease in ENGAGE) in the both studies. These finding suggested that both Aβ and tau could influence each other, and Aβ immunotherapy could improve tau pathology. The most common adverse effect was amyloid related imaging abnormalities (ARIA; ARIA-E: suggestive of vasogenic edema and sulcal effusions; ARIA-H: suggestive of hemosiderin deposits). These occurred in about 35% of the treated patients in both studies at the highest dose.

Regulatory authorities in the U.S., EU and Japan responded differently to aducanumab. The FDA approved aducanumab under the agency's accelerated approval pathway in 2021.[6] Although the results of the two phase 3 studies were inconsistent with respect to efficacy of slowing cognitive decline, the FDA has determined that there is substantial evidence that aducanumab consistently reduces Aβ plaques in the brain and that the reduction in these plaques is reasonably likely to predict important benefits to patients. On the other hand, European Medicines Agency (EMA) and Ministry of Health, Labour and Welfare (MHLW) in Japan rejected marketing application for aducanumab.[19,20] These authorities have concluded that the link between reduction of Aβ plaques in the brain and slowing cognitive decline had not been established in the two phase 3

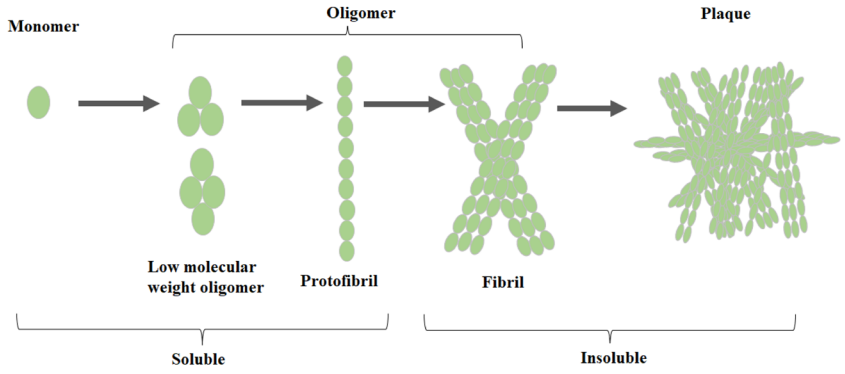

Fig. 2. General Aggregation Scheme of Aβ from Monomers to Plaque

studies, and the benefits of aducanumab did not outweigh the risk of ARIAs.

Later, Biogen announced that it would stop marketing aducanumab and terminate phase 4 study (ENVISION) to verify clinical benefit of aducanumab, due to realigning resources for AD franchise at Biogen.[21] The rights to aducanumab will revert to the originator, Neurimmune.

2.3. Lecanemab Lecanemab, a humanized form of the mAb158 mouse antibody, was originally discovered at Uppsala University and is being developed by Eisai and Biogen. This antibody was designed to preferentially capture Aβ protofibrils.[22] The rationale came from the pathology of Swedish-type inheritable AD (Arctic mutation),[23] where carriers of the Arctic mutation (E693G in APP) showed decreased Aβ monomer levels in plasma but enhanced formation of protofibrils in the brain. The evidence suggested that Aβ protofibrils could be a primary pathogenic form of AD, and antibodies targeting protofibrils might have superior therapeutic properties. In a large phase 3 study (Clarity AD) for early AD patients, a 10 mg/kg dose of lecanemab every 2 weeks reduced Aβ plaques by about 60% based on the amyloid PET study and resulted in a significant reduction in the CDR-SB score by 27% at 18 months. Secondary endpoints also reflected the CDR-SB scores thus slowing cognitive decline or improving functional measures. ARIAs were observed in about 20% of the patients, which were higher frequency among apolipoprotein E (ApoE) ε4 carriers and patients with microhemorrhage in the brains. The occurrence of ARIAs in lecanemab was less than those observed in aducanumab.[8] Like aducanumab, phosphorylated tau related biomarkers were significantly reduced.[24] Based on these promising findings, lecanemab was granted traditional approval by the FDA as a treatment for AD in July 2023.[7] Also, lecanemab has been approved by the MHLW in Japan as a treatment for slowing progression of MCI and mild dementia due to AD.[8]

2.4. Donanemab Donanemab is a humanized antibody with selective affinity to N-terminally truncated and pyroglutamate-modified Aβ (AβpE3). A part of the Aβ monomer is subjected to N- and/or C-terminal modification, and AβpE3 was identified in sufficient quantities as an N-truncated Aβ variant in Aβ plaques derived from postmortem AD brains, indicating that AβpE3 could be a pathogenetic form of AD.[25] Thus, donanemab was designed to remove existing Aβ burdens in the brain. AβpE3 peptides are also known to form stable and soluble oligomers and induced neurodegeneration in AD mouse models.[26] Eli Lilly announced a positive finding for donanemab in a phase 3 study,[27] where it showed a significant reduction of Aβ plaques in the brain by about 80% based on amyloid PET imaging and reduced the CDR-SB score by 35% compared with the placebo at 18 months (700 mg for the first three doses and 1400 mg thereafter at every 4 weeks). Also, significant reduction in phosphorylated tau related biomarkers was observed. During the phase 3 study, treatment related ARIAs were frequent and observed in about 35% of the patients,[9] which was similar to or less than those observed in aducanumab.[6] The data encouraged the start of global regulatory submissions, and Eli Lilly has completed submission for full approval to the FDA in July 2023 and the MHLW in September 2023.[28,29]

2.5. Future Directions for Aβ Antibodies Solanezumab, selectively targeting Aβ monomers, failed to reduce Aβ plaques and slow cognitive decline in a phase 3 study,[30] most likely because monomers might not be the right target among the Aβ species. Indeed, Aβ monomers were reported to be physiologically important but not a pathological form of AD.[31] On the other hand, there were several clinically investigated antibodies having high affinity for Aβ oligomers, other than aducanumab and lecanemab; however, all of them failed to show clinical benefits[4] (Table 1). For example, bapineuzumab and gantenerumab can bind a broad range of the Aβ species,[17,32] and crenezumab has preferential affinity for Aβ oligomers as well as Aβ monomers.[33] A plausible reason for such unsatisfactory clinical outcomes could be a competitive binding with Aβ monomers. Indeed, Aβ monomers exist abundantly in both the brain and its periphery, and most of such antibodies can be captured by these monomers, which would lead to a significant decrease in efficacy levels over Aβ oligomers.[34] Taken together, high selectivity for Aβ oligomers with low affinity for monomers appear to be a crucial profile for an Aβ antibody to be useful for AD therapeutics. As noted above, soluble oligomers of Aβ exhibited selective toxicity in cells and could be involved in AD pathogenesis, which is also the basis for suggesting that Aβ oligomers are one of the primary targets for Aβ antibodies.

Peripheral administration is not conductive to delivering an antibody to the brain at a sufficiently high dose due to low blood–brain barrier (BBB) penetration (approx. 0.1% of injected dose in general).[35] Therefore, antibodies engineering to achieve enhanced BBB crossing have been attracting. Such engineered antibodies are expected to improve clinical efficacy and reduce dosages, which could contribute to ameliorating side effects, such as ARIAs.[36] One example to achieve high BBB penetration is Denali's Antibody Transport Vehicle (ATV) technology. The transferrin receptor is responsible for

Table 1. Representative Aβ Antibodies Investigated in Clinical Study (As of 10 January, 2024)

Drug	Company	Target Aβ species	Patient population	Outcome
Solanezumab	Eli Lilly	Monomer	Mild to moderate AD	Lack of efficacy
Bapineuzumab	Elan/Pfizer/Johrnson&Johrnson	Monomer, oligomer, plaque	Mild to moderate AD	Lack of efficacy
Gantenerumab	Hoffman LaRoche	Monomer, oligomer, plaque	Mild to moderate AD	Lack of efficacy
Crenezumab	AC Immune/Hoffman LaRoche	Monomer, oligomer	MCI to mild AD	Lack of efficacy
Aducanumab	Biogen/Eisai	Oligomer	MCI to mild AD	Slowed cognitive decline
Lecanemab	Biogen/Eisai	Oligomer (protofibril)	MCI to mild AD	Slowed cognitive decline
Donanemab	Eli Lilly	Oligomer (AβpE3)	MCI to mild AD	Slowed cognitive decline

MCI: mild cognitive impairment due to AD. Progression of AD: preclinical AD → MCI → mild AD → moderate AD → severe AD.

the transport of iron into the brain to maintain iron homeostasis. Therefore, an antibody with a transferrin receptor 1-binding domain can bind to receptors on endothelial cells, which enables to penetrate the BBB through active receptor-mediated transport[37] (Fig. 3). Biogen announced the leveraging of ATV technology to develop next generation Aβ antibodies to increase brain exposure along with reduced ARIAs.[38] Eisai also announced that they are investigating the application of their original brain transport technology to develop the next-generation lecanamab.[39] Likewise, Roche developed the Brainshuttle technology in which a Fab antibody fragment can bind transferrin receptor 1. Indeed, their new antibody trontinemab, gantenerumab with the Brainshuttle, improved BBB crossing and cleared Aβ plaques with fewer ARIAs.[40] Detailed investigations on brain-penetrating Aβ antibodies using such technologies could help understand the mechanism behind ARIAs along with significant reduction in dosage, thus providing affordable treatment options for AD. If a low dose and brain-penetrating Aβ antibody can be confirmed to be safe, long-acting injection formulation may be used to increase the convenience of patients and caregivers.

The adverse effects of ARIAs shown above and issues on the affordability of Aβ antibodies[41] encourage reconsideration of small molecule inhibitors for the two enzymes, BACE1 and γ-secretase responsible for Aβ production (Fig. 1), as maintenance therapy after treatment with Aβ antibodies, once Aβ plaques or oligomers have been cleared.[42,43] All clinical trials on BACE1 inhibitors were discontinued due to the occurrence of adverse events, which include cognitive impairment likely derived from the cleavage of other substrates, particularly SEZ6 that is involved in synaptic plasticity.[44,45] However, BACE1 inhibitors having selectivity over BACE2 could ameliorate this adverse event.[46,47] Modulators of γ-secretase are also being reconsidered as they can curb the Notch-interfering ability of γ-secretase inhibitors. Indeed, scientists at Roche reported on RG6289, which inhibited Aβ40 and Aβ42 production without affecting total Aβ production and showed a safe profile with only mild adverse events. On the basis of the promising profiles observed in the phase 1 study, Roche plans to initiate a phase 2 study.[44] Clinical trials to confirm the potential of maintenance therapy with BACE1 inhibitors and γ-secretase modulators should be considered to provide another option for patients and caregivers to address the issues of immunotherapy.

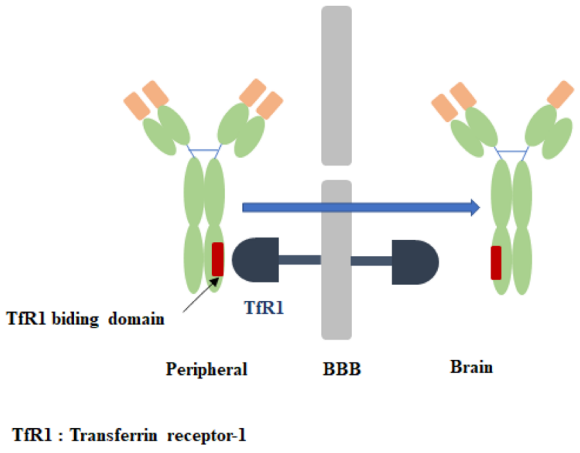

Fig. 3. Overview of Denali's Antibody Transport Vehicle

3. Anti-tau Therapies for AD

3.1. The Tau Hypothesis Tau is a microtubule-associated protein encoded by the microtubule-associated protein tau (MAPT) gene, which is abundant in the brain.[48,49] There are six tau isoforms in the adult human brain, which are differentially expressed during development.[50] Physiologically, tau plays a key role in maintaining the structure and stability of neuronal axons. In dendrites, it supports the spine remodeling necessary for synaptic plasticity.[51] The physiological functions of tau are modulated by the proper maintenance of modifications such as phosphorylation and acetylation. On the other hand, when excessive modifications occur, tau loses its ability to bind to microtubules, undergoes structural changes, and forms aggregates and neurofibrillary tangles containing NFTs[52] (Fig. 4). NFTs are a major pathological hallmark of AD, in which tau fibrillates and deposits in the cytoplasm,[52,53] resulting in microtubule destabilization, impairment of synaptic function and morphology, and neurodegeneration.[54] Importantly, the presence of tau is required for Aβ-induced neurotoxicity and cognitive dysfunction.[55,56] Likewise, associations between the onset of AD symptoms and the development of NFTs were found in clinical situations. For example, asymptomatic subjects with Aβ accumulation (amyloid PET positive) but not NFTs (tau PET negative) did not show cognitive decline over at least 3 to 5 years, while asymptomatic subjects who were both amyloid and tau PET positive showed continuously cognitive worsening.[57] More importantly, tau aggregation correlates well with cognitive deficit,[58] suggesting

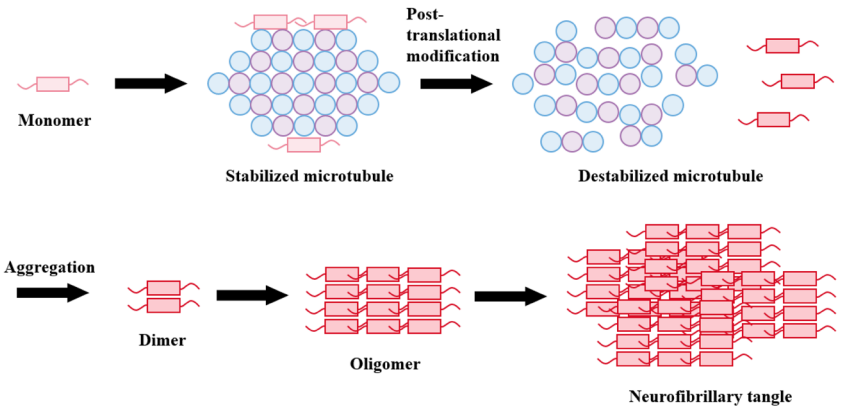

Fig. 4. General Aggregation Scheme of Tau

Table 2. Tau-Targeted Drugs (As of 10 January, 2024)

Drug name	Company	Molecule type	Mechanism of action	Patient population	Trial phase
Tideglusib	Noscira	Small molecule	GSK3β inhibitor	Mild to moderate AD	Terminated due to lack of efficacy
LY3372689	Eli Lilly	Small molecule	O-GlcNacase inhibitor	Early AD	Phase II, ongoing
TRx0237	TauRx Therapeutics	Small molecule	Aggregation inhibitor	Mild to moderate AD	Phase III, ongoing
E2814	Eisai	Antibody	Inhibition of tau protein	Early onset Alzheimer's disease caused by a genetic mutation	Phase II/III, ongoing
Bepranemab	Hoffmann-La Roche /UCB	Antibody	Inhibition of tau protein	MCI to mild AD	Phase II, ongoing
PRX005	Bristol-Myers Squibb/ Prothena	Antibody	Inhibition of tau protein		Phase I, ongoing
Gosuranemab	Biogen	Antibody	Inhibition of tau protein	MCI to mild AD	Terminated due to lack of efficacy
Semorinemab	Hoffmann-La Roche /AC Immune	Antibody	Inhibition of tau protein	MCI to mild AD	Terminated due to lack of efficacy
Tilavonemab	AbbVie	Antibody	Inhibition of tau protein	Early AD	Terminated due to lack of efficacy
Zagotenemab	Eli Lilly	Antibody	Inhibition of tau protein	Early AD	Terminated due to lack of efficacy
AADvac1	Axon Neuroscience	Vaccine	Inhibition of tau protein	Mild AD	Phase II, completed
ACI-35030	AC Immune	Vaccine	Inhibition of tau protein	Early AD	Phase I/II, ongoing
BIIB-080	Biogen	Antisense oligonucleotide	Reduction of tau protein	MCI to early AD	Phase II, ongoing
NIO-752	Novartis	Antisense oligonucleotide	Reduction of tau protein	Early AD	Phase I, ongoing

MCI: mild cognitive impairment due to AD.

tau aggregation could be a pathological cascade of AD, or Aβ and tau could work in an integrated manner to progress AD pathology.[59] Considering these points, tau-targeting therapeutics have been actively developed to slow or halt the progression of AD (Table 2). In this review, we provide updates on small molecules such as tau modification and aggregation inhibitors, immunotherapies, and antisense oligonucleotides that have advanced into clinical development.

3.2. Tau Modification Inhibitors In AD, the physiological function of tau is thought to be lost when it undergoes excessive post-translational modifications.[50] Therefore, several modification inhibitors have been developed. For example, small molecules targeting glycogen synthase kinase 3β (GSK3β) have been well investigated. GSK3β is involved in tau hyperphosphorylation and promoting tau aggregation.[60] One GSK3β inhibitor, tideglusib, was found to be safe and prevented brain volume loss in a phase 2 trial but did not meet the primary endpoint for cognitive function.[61] Several companies have pursued GSK3β inhibitors, but no compound is currently in clinical development.[62] O-GlcNAcase is the enzyme responsible for the hydrolysis of the O-linked β-*N*-acetyl glucosamine (O-GlcNAc), and O-GlcNAc inhibitors are in clinical trial by several companies to intervene in the post-translational modification of tau. Because O-GlcNAcylation and phosphorylation can crosstalk *via* tau protein,[63] the predominance of tau O-GlcNAcylation by O-GlcNAcase inhibitors is considered to prevent hyperphosphorylation.[64] At present, LY3372689 is the only compound in phase 2 trials, where safety, tolerability, and efficacy are being investigated.[65]

3.3. Tau Aggregation Inhibitors When tau undergoes modifications such as phosphorylation and acetylation, it is thought to form aggregates which leads to neurodegeneration. The tau protein aggregation inhibitor TRx0237, also known as methylene blue, is currently in the clinic.[66] Methylene blue reduced aggregates and ameliorated deficits in a variety of behavioral phenotypes in two tau preclinical models.[67] More recently, a compound preventing the early stages of tau aggregation was discovered, and a phase 1 trial is underway.[68,69]

3.4. Immunotherapies Tau aggregates in cells are considered to cause neurodegeneration, and some tau species are known to spread among cells *via* different cell types and pathways.[70] Immunotherapies targeting to the prevention of tau seeding and propagation have been investigated. Indeed, regarding passive immunization, antibodies against various epitopes have been advanced. Unfortunately, multiple antibodies targeting the N-terminal epitope have failed to show clinical benefit.[71–73] Recently, the microtubule binding region (MTBR)-tau has been found to correlate well with AD pathology and clinical progression.[74] Antibodies targeting MTBR-tau inhibited seed aggregation in cellular assays and tau accumulation in mice injected with brain extracts from AD patients.[75,76] Increasing evidence on MTBR-tau provided the opportunity to initiate efforts on exploring antibodies targeting MTBR-tau. A major advancement has been the development of E2814, a MTBR-tau antibody discovered as part of a collaboration between University College London and Eisai, E2814 showed target engagement with tau in the CSF, with no significant adverse events related to the drug being observed.[77] E2814 was chosen to be evaluated in the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), investigating both single and combination therapy with lecanemab for asymptomatic and symptomatic participants.[78] Other antibodies targeting MTBR and nearby tau, such as PRX005 or bepranemab, were shown to be safe with dose-dependent exposure in the plasma and CSF, and phase 1 and phase 2 studies are ongoing. On the other hand, clinical trials of many anti-tau antibodies missed their primary endpoints, gosuranemab, semorinemab, tilavonemab, and zagotenemab which can act in the extracellular region.[74] For active immunotherapy (tau vaccine), clinical studies of AADvac1 and ACI-35030 are ongoing, and of particular interest is AADvac1.[68,79] In a phase 2 study, AADvac1, designed to target N-terminally truncated tau, was found to be safe and well tolerated with a significant reduction in blood neurofilament light chain (NfL) levels and a tendency of a decline in levels of total tau and p-tau in the CSF. In the clinical study, the whole analysis failed to show cognitive benefit, while a *post hoc* analysis predicted positive results for patients with both Aβ and tau positive.[80]

3.5. Antisense Oligonucleotides Antisense oligonucleotide (ASO) technology targeting human MAPT mRNA to

decrease the expression of tau also has therapeutic potential. Two ASOs BIIB080 and NIO752 were tested for effects on AD.[81,82] In non-clinical studies, BIIB080 inhibited tau aggregation in cellular assays, reduced mRNA and protein levels in transgenic mice, and suppressed neurodegeneration and cognitive decline.[83] In a phase 1b study, BIIB080 reduced both CSF tau and tau aggregation.[84] Also, BIIB080 showed favorable trends on cognitive function, where the CDR-SB score of participants in high-dose groups tended to be declined relative to those in low-doses and placebo groups.[85] Further clinical studies will clarify clinical benefit of BIIB080 for mild cognitive impairment or mild dementia due to AD. Another tau ASO NIO752 is in phase 1 clinical studies, and the results have not been disclosed yet.

3.6. Future Directions for Anti-tau Therapies Many clinical trials of tau aggregation inhibitors have failed to show clinical benefits, although O-GlcNAcase inhibitors are in clinical testing to examine their potential. Targeting tau aggregation through post-translational modification might be inappropriate as it is difficult to selectively capture pathological forms of tau. A tau ASO has shown a positive trend on cognitive functions along with reduction in biomarkers related to tau, indicating a potential to be anti-tau therapeutics. Also, a tau vaccine, AADvac1, showed functional benefits in the clinic and is awaiting completion of a phase 2 study to see whether it can meet the primary endpoint, which would assess the potential of this approach. Although anti-tau antibodies have experienced many failures, some antibodies, such as E2814, exhibited functional benefits reducing tau levels. Considering that the failed antibodies targeted N-terminal fragments, the MTBR region could be a relevant target for anti-tau antibodies. Nevertheless, thorough investigation on the selection of the epitope should be a key to successfully targeting pathological tau. Tau antibodies also face common challenges with Aβ antibodies, *e.g.*, crossing the BBB. Although drug-related adverse events are limited with tau antibodies, improved brain penetration is needed to enhance efficacy. Also, clinical studies must select the suitable patient populations based on clinical stages and pathogenesis. Finally, combination therapy of tau antibodies with Aβ antibodies could be appropriate as both Aβ and tau are likely to be involved in the pathogenesis of AD.

4. Conclusion and Perspectives

Although lecanemab, and donanemab have achieved remarkable success in the clinical developments for treating AD, their clinical effects for symptomatic patients have been relatively moderate. The growing consensus is that more efficient intervention with Aβ antibodies and anti-tau drugs should be able to prevent or delay the onset of AD in asymptomatic individuals having Aβ and tau pathology, because accumulation of Aβ plaques precede symptom onset by 10–20 years. The National Institute on Aging and the Alzheimer's Association (NIA-AA) published a draft of revised clinical guidelines to recommend the diagnosis and staging of AD by abnormalities on Aβ and tau biomarkers, regardless of the presence or absence of cognitive impairment.[86] Most of the therapeutics have been investigated with symptomatic patients so far, and more clinical investigations are needed on Aβ antibodies or anti-tau drugs for asymptomatic (preclinical AD) patients. Considering the timing of accumulation of Aβ and tau, it should lead to more feasible clinical trials in terms of cost, duration, and the number of patients. Indeed, lecanemab and donanemab have been in clinical trials for preclinical AD,[87,88] and E2814, a MTBR-tau antibody, will be also investigated for preclinical AD.[89]

As discussed above, selective targeting of Aβ oligomers or fibrillar Aβ plaques, which are the plausible pathogenic forms, and avoiding binding to Aβ monomers could be keys to functional and cognitive benefits. Understanding the mechanism behind ARIAs is required to increase the clinical benefit of Aβ antibodies. Regarding tau-targeting therapies, anti-tau antibodies look promising as they offer functional benefits in clinical use. Like Aβ antibodies, the choice of the epitope is important to reduce pathological tau leading to significant efficacy. Targeting the MTBR region could be ideal considering the functional efficacy observed with E2814. The ongoing clinical trials for tau ASOs and tau vaccines should determine their potential. A common challenge for Aβ and tau antibodies is crossing the BBB to increase both efficacy and safety. One promising approach to deliver antibodies to the whole brain is a technology leveraging receptor mediated active transport. Also, maintenance therapy using BACE1 inhibitors or γ-secretase modulators after immunotherapy offers another treatment option to address the issues of ARIAs and the affordability of antibodies. Finally, combination of Aβ antibody with anti-tau therapeutics could deliver synergetic clinical benefits. Aducanumab, lecanemab, and donanemab reduced tau or neurofibrillary tangles along with Aβ plaque reduction, suggesting the interplay between the Aβ and tau pathways thus pointing to the relevance of combination therapy. The finding of the DIAN-TU study to investigate combination effects between E2814 and lecanemab are eagerly awaited.

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Conflict of Interest N. S., T. H., M. I., and K. K. are employees of Shionogi & Co., Ltd.

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