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Detection and treatment of Alzheimer's disease in its preclinical stage

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Abstract

Longitudinal multimodal biomarker studies reveal that the continuum of Alzheimer's disease (AD) includes a long latent phase, referred to as preclinical AD, which precedes the onset of symptoms by decades. Treatment during the preclinical AD phase offers an optimal opportunity for slowing the progression of disease. However, trial design in this population is complex. In this Review, we discuss the recent advances in accurate plasma measurements, new recruitment approaches, sensitive cognitive instruments and self-reported outcomes that have facilitated the successful launch of multiple phase 3 trials for preclinical AD. The recent success of anti-amyloid immunotherapy trials in symptomatic AD has increased the enthusiasm for testing this strategy at the earliest feasible stage. We provide an outlook for standard screening of amyloid accumulation at the preclinical stage in clinically normal individuals, during which effective therapy to delay or prevent cognitive decline can be initiated.

AD is a progressive neurodegenerative disease characterized by the neuropathologic findings of amyloid-β (Aβ) plaques, neurofibrillary tau tangles and neurodegeneration resulting in dementia[1]. AD is now generally considered to be a seamless continuum that encompasses three broad stages: the 'preclinical' or presymptomatic stage, lasting over a decade, during which individuals are asymptomatic yet harbor AD neuropathology; the 'prodromal' stage, during which individuals have impairment in at least one cognitive domain but maintain good function; and the more familiar 'dementia' stage, in which multiple cognitive domains are affected with an accompanying decline in daily function[2] (Fig. 1). These abnormalities are associated with a pathophysiological cascade that results in cytoskeletal changes and neuronal dysfunction with subsequent degeneration and brain atrophy[3,4].

The neuropathologic features of AD begin 15–20 years before obvious cognitive symptoms in both sporadic and genetic forms of AD[5-7]. These changes can now be accurately and reliably detected by cerebrospinal fluid (CSF) assays, brain positron emission tomography

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(PET) imaging and, most recently, by plasma biomarker assays. Preclinical AD may be divided into ‘presymptomatic’ and ‘asymptomatic at risk’ (ref. 8). ‘Presymptomatic preclinical AD’ refers to the state of individuals with genetic forms of AD who will develop AD in the future. Individuals with presymptomatic preclinical AD initially show no overt clinical symptoms but have at least one mutation in the familial AD (fAD) genes (amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*)) or have trisomy 21 (Down syndrome (DS)) with its resultant extra copy of the *APP* gene. In all cases of genetically determined AD, there is overproduction and hence accumulation of brain Aβ. ‘Asymptomatic at risk’ may be used to define preclinical AD in individuals in the general population without clinical symptoms but who are positive for AD biomarkers, which are elevated brain Aβ as visualized by PET or, in the CSF, decreased $A\beta_{42}$ and increased phosphorylated tau (p-tau) species as well as total tau protein[8]. Data from longitudinal studies indicate that individuals with elevated brain Aβ (that is, preclinical AD) are at a heightened risk for developing cognitive symptoms consistent with dementia on the Clinical Dementia Rating (CDR) scale with long-term follow-up[9], suggesting that the preclinical state represents a stage of AD rather than being at risk for developing AD. That is, the presence of Aβ pathology is not merely a risk factor but rather a manifestation of disease[10]. Therefore, treatment during the preclinical AD stage offers an ideal opportunity for slowing the progression of AD, as the absence of symptoms suggests that extensive irreversible damage is limited. However, trial design in this population is complex for several reasons, including tracking cognitive change in asymptomatic individuals and identification of individuals who are asymptomatic but have elevated brain amyloid[11].

Food and Drug Administration (FDA) guidance on developing drugs for ‘early AD’ has been an important catalyst for the development of clinical trial designs for earlier stages of AD. In its 2018 guidance for industry[12], the FDA considers that AD biomarker change may form the basis for accelerated approval, while meeting both biomarker and cognitive endpoints will be necessary to receive full approval[12]. The FDA also recommends that sponsors conduct studies of sufficient duration to evaluate patients as they transition to the next defined AD stage. Aβ reduction is considered ‘reasonably likely to confer clinical benefit’ and is designated by the FDA as a suitable surrogate endpoint for AD clinical trials. Therefore, reduction of Aβ alone is now considered sufficient to obtain accelerated approval for AD interventions. Post-marketing studies supporting clinical benefit are required for full approval.

In this Review, we aim to discuss recent advances in plasma biomarkers, new approaches to recruitment, sensitive cognitive instruments and self-reported outcomes that have facilitated the successful launch of multiple phase 3 trials for preclinical AD. We will also highlight the recent success of anti-Aβ immunotherapy trials in symptomatic AD, which have increased the enthusiasm for testing this strategy at the earliest feasible disease stage. Finally, we provide an outlook for standard screening for Aβ accumulation in the aging population with effective therapy to delay or prevent cognitive decline.

Definition of preclinical AD along the AD continuum

Autopsy evidence

Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Aging (ABLE), among others, have provided converging evidence that biomarker abnormalities consistent with the AD pathophysiological process are detectable before the emergence of overt clinical symptomatology and are, in fact, highly predictive of subsequent cognitive decline. Both Aβ PET and CSF studies suggest that a substantial proportion of clinically normal older individuals demonstrate evidence of elevated brain Aβ[13-16], ranging from approximately 20% to 40%, which is consistent with large postmortem series[17,18]. Interestingly, the percentage of 'Aβ-positive' cognitively normal individuals at autopsy detected at a given age appears to closely parallel the percentage of individuals diagnosed with AD dementia a decade later[19,20]. Similarly, genetic at-risk cohorts demonstrate evidence of elevated brain Aβ many years before detectable cognitive impairment[9,21-25].

Controversy: does Aβ accumulation inevitably lead to symptomatic AD?

Multiple longitudinal studies have also consistently found that cognitively normal individuals with elevated brain Aβ display, in general, accelerated cognitive decline compared to individuals with normal brain Aβ levels[26-32]. Nonetheless, the question as to whether all individuals with elevated brain Aβ will develop AD dementia if they live long enough is difficult to answer. The approximately 10-year delay between accumulation of brain Aβ and the onset of early cognitive impairment, along with the variability in associated cognitive decline, lead to a small percentage of cognitively normal adults with high levels of Aβ who may not experience cognitive decline or dementia[33]. Across studies, however, those individuals showing abnormalities in both Aβ and additional biomarkers demonstrate more rapid cognitive decline than individuals with no elevation in brain Aβ with respect to their cognitive trajectories over the subsequent decade[34-36].

Genetic forms of AD

Autosomal dominant AD

Aside from the sporadic form, AD can also occur because of dominantly inherited mutations. Mutations in the *APP* gene (located at chromosome region 21q21.2), *PSEN1* (located at 14q24.3) or *PSEN2* (located at 1q42.13) lead to fAD. fAD accounts for <1% of all AD cases and presents as a classic Mendelian autosomal dominant disease, usually with an early (<65 years) age of onset. Individuals carrying presymptomatic mutations have provided important clues on biomarker trajectories associated with the preclinical state of the disease[6]. They also represent an important population in which to investigate the efficacy of disease-modifying agents in delaying clinical onset of the disease, as it is possible to estimate when the clinical signs of the disease will appear based on the family history of the carriers, the so called 'estimated year of onset' (ref. 6). These familial cases of AD appear to have the same clinical and pathologic phenotypes as sporadic cases[37].

DS

People with trisomy 21 (DS) represent the world's largest population of genetically determined AD[7]. DS is not a familial form of AD and therefore is not considered part of the 1% represented by fAD. There are approximately 250,000 persons with DS in the USA, representing approximately 4% of the 6.5 million people with AD in the USA[38]. AD pathology has been described in all adults with full trisomy 21 by the age of 40 years, and its hallmarks are qualitatively similar to those of sporadic AD. Evidence from biomarker studies also suggests that the pathophysiology of the disease in DS is similar to that of the sporadic and autosomal dominant forms of AD[7,39]. Several studies of individuals with DS have assessed Aβ brain deposition with PET tracers, studied plasma and CSF biomarkers or described the atrophy and cerebral metabolic patterns of AD[40-44]. These changes begin more than a decade before the onset of dementia, in a strikingly similar order and timing as those described for autosomal dominant AD[6,25,45].

Several clinical trials for AD have been conducted in the population with DS[46,47]. Clinical trials conducted in this population have obvious advantages: the ultra-high risk for developing symptomatic AD and a predictable sequence of events that make this population ideal for prevention trials for AD[48].

The amyloid, tau and neurodegeneration (ATN) staging framework

Besides the clinical staging of symptomatic AD, it is now possible to stage patients based on pathology using the ATN framework (Table 1). The cascade of changes in biomarkers that occurs over the AD continuum has been used to define pathological stages of the disease and is referred to as the ATN framework: 'A' refers to amyloid pathology, 'T' refers to tau pathology, and 'N' refers to neurodegeneration[49,50]. Evaluation of elevated brain Aβ can be performed by use of Aβ PET imaging, CSF measures of Aβ peptides and, most recently, plasma measurements. Additionally, tau pathology in neurofibrillary tangles can be assessed with PET imaging, while total tau as well as its various phosphorylated forms can be measured in both CSF and in plasma. Neurodegeneration can be assessed with fluorodeoxyglucose (FDG) PET imaging and magnetic resonance imaging (MRI), while measurements of neurofilament light (NfL) in the CSF and plasma have been shown to reflect brain atrophy to a certain extent. This framework is being applied across the spectrum of AD including its preclinical stage[51,52]. The ATN framework allows for targeting the appropriate mechanism at each disease stage and has been shown to aid in providing accurate diagnosis and prognosis[53-55] (Fig. 2). With this framework, there is the challenge of dichotomization across various biomarkers and determining cutoffs for each category, and it continues to be refined[56].

The ATN framework is imperfect in its predictive ability due to the large variability in rate of progression among individuals[57]. In addition, it leaves room for choice of biomarker and for determining specific thresholds for positivity. Different biomarker modalities and cutoffs can result in different categorizations of individuals. Nevertheless, the ATN framework provides an important and useful starting point as we consider anchoring the clinical phenotype of AD across its spectrum with objective biomarkers of pathology.

Amyloid pathology burden

Several longitudinal follow-up studies have examined the role of AD neuroimaging and biofluid biomarkers to predict subsequent decline in cognition among cognitively normal individuals[58-69].

Clinically normal individuals with elevated brain Aβ demonstrate multiregional brain atrophy[70,71], cortical thinning[72-74], aberrant default network activity and functional MRI connectivity deficits similar to AD[75,76], decreased task-induced functional MRI deactivation in the default network regions[75], lower performance on a demanding test of associative memory retrieval[76] and episodic memory deficits[77] as well as longitudinal cognitive decline[31]. Aβ deposition occurs in the neocortical areas of the brain, one of the first areas affected due to preclinical AD pathology. Across three independent samples of cognitively normal older adults, it has been reported that lower thresholds for Aβ PET in the Centiloid (CL) range of 15.0 to 18.5 are predictive of future Aβ accumulation and cognitive decline. This range appears to correspond to an inflection point in the Aβ PET distribution beyond which Aβ and cognitive trajectories diverge from normal[67]. For CSF, an $A\beta_{42}/A\beta_{40}$ ratio of ≤0.062 is considered abnormal[68].

Low levels of $A\beta_{42}$ in CSF reflect higher levels of Aβ plaques, and CSF biomarkers have been found to have good predictive ability for memory decline in clinically normal individuals and are thought to represent one of the earliest changes reflecting AD pathology in the brain[65].

Recent work on immunoassays of plasma biomarkers of AD has demonstrated their ability to confirm AD pathology in the brain and to improve prediction of cognitive decline in cognitively unimpaired older populations[78-83]. Assessment of the plasma $A\beta_{1–42}/A\beta_{1–40}$ ratio by mass spectrometric methods has now been identified as a sensitive and specific indicator of brain fibrillar Aβ load as determined by Aβ PET. Immunoassays and mass spectrometry measurements of p-tau species, particularly p-tau217 and p-tau231, are also excellent markers of AD pathology[84,85].

In preclinical AD, plasma p-tau217 in combination with either plasma $A\beta_{42}$ or $A\beta_{40}$ has demonstrated excellent accuracy in predicting elevated brain Aβ[86,87]. Many of these plasma biomarkers are being implemented in clinical trials for preclinical AD (for example, the AHEAD trial of lecanemab in preclinical AD) to assist with enriching for cognitively normal individuals who are likely to have elevated brain Aβ[88].

Tau pathology burden

The hyperphosphorylated paired helical filament that forms neurofibrillary tangles quantified by Braak stages is better correlated with AD severity and neuronal atrophy than Aβ plaques. Both tau and p-tau are increased in AD pathology and are considered to be a measure of neuronal injury. Longitudinal tau PET cohorts in patients with high-risk preclinical AD have provided an understanding of the spatial distribution of neurofibrillary tangles that can allow for staging neurodegeneration according to tau levels in preclinical AD[89]. Recent work indicates that tau PET may also be an excellent predictor of subsequent cognitive decline in preclinical AD cases[10].

Estimates of tau positivity in clinically unimpaired individuals with elevated Aβ vary depending on whether positivity is based on the medial temporal cortex (15%) or the entorhinal cortex alone (40%). Recent work has demonstrated the presence of divergent patterns of tau aggregation in individuals with preclinical AD, which has important implications for participant selection and evaluation of disease modification in prevention trials. Specifically, while the entorhinal cortex has a central role in the early appearance of tau, it may be the inferior temporal cortex that is the critical region for rapid tau accumulation in preclinical AD[90]. Plasma p-tau181 (ref. 84) and p-tau217 have shown excellent accuracy in predicting elevated brain Aβ in asymptomatic individuals[91] as well as subsequent cognitive decline.

Neurodegeneration or neuronal injury

Reductions in regional cerebral glucose metabolism as measured by FDG PET appear to precede the onset of AD symptoms in predisposed individuals, in both genetic early-onset and late-onset AD forms[92]. Pre-symptomatic persons carrying autosomal dominant genetic mutations associated with early-onset fAD (onset age < 65 years) show the typical AD pattern of hypometabolism compared to age-matched mutation non-carriers[93]. By monitoring progression to mild cognitive impairment (MCI) and dementia among cognitively normal older people, these studies showed that reductions in regional cerebral glucose metabolism precede the onset of cognitive decline by many years[94] and predict cognitive decline from normal cognition to cognitive impairment with over 80% accuracy[95]. However, it should be noted that the specificity of hypometabolism for AD is confounded by other potential neurodegenerative diseases that may underlie cognitive decline.

PET imaging of SV2A, a presynaptic protein involved in neuro-transmitter release and storage, may serve as a method to quantify functional synapses and, thus, to estimate synaptic density[96]. Synaptic PET imaging targeting SV2A may provide another biomarker for neurodegeneration in the ATN framework that more closely tracks the progression of the disease and cognitive impairment and is less sensitive to confounding factors such as blood glucose level, stimulation and medication, which affect FDG PET[97]

NfL and neurogranin (Ng) are promising candidate AD biomarkers, reflecting axonal and synaptic damage, respectively. CSF NfL and Ng concentrations are increased in cognitively normal older adults with biomarker evidence of tau pathology and neurodegeneration[98]. Elevated NfL chain levels correlate with AD progression[99]. Combinations of plasma biomarkers are being validated as diagnostic and prognostic tools in population-based cohorts including preclinical AD[100].

The most direct method of visualizing and quantifying regional brain neurodegeneration is using MRI volumetrics. Although limited in applicability in preclinical AD[101], much work has demonstrated hippocampal atrophy as being helpful in predicting subsequent cognitive decline across the spectrum of AD[102-104].

It is worth noting that recent advances in plasma biomarkers, while not currently available in clinical practice, are being rapidly implemented in clinical trials, especially in prevention trials to enrich the sample with individuals who harbor AD brain pathology. Plasma

biomarkers are also being validated beyond screening tests but also as potential outcome measures[91] and represent a class of biomarkers that is cost effective and much more scalable than PET and CSF-based biomarkers.

Cognitive-assessment measures in preclinical AD

Slight but measurable cognitive decline has been reported during preclinical AD. Both retrospective and prospective studies of cognitively normal individuals who subsequently progressed to AD dementia have found episodic memory decline to be a defining feature of preclinical AD[105,106]. Sensitive cognitive measures for use in preclinical AD have been developed and validated. These include the Preclinical Alzheimer's Cognitive Composite[107-109], the Alzheimer's Prevention Initiative Composite Cognitive Test[110,111] and the Repeatable Battery for the Assessment of Neuropsychological Status. Each of these assessment tools includes measurement of episodic memory and executive function. These scales have been shown to be useful in detecting AD for clinical trial purposes as they allow for accurate longitudinal measurement of subtle cognitive decline associated with AD.

The Cognitive Function Instrument (CFI) is a 14-item assessment of cognitive status that can be completed by participants or a study partner. Both participant and study partner CFI scores are good predictors of cognitive decline in individuals with normal cognition[112,113]. While baseline values among the cognitively healthy might be a marker of the risk to progress, change scores including those from study partners appear to be useful outcome measures in predicting decline among individuals with some impairment. Importantly, the CFI administered to the participant appears to be a better initial predictor of decline than study partner CFI in the cognitively normal group[113]. The CFI score is used as a key secondary outcome in preclinical trials, as a treatment benefit on the CFI would support a clinically meaningful effect.

The ADL Prevention Instrument was designed to detect early impairment of the activities of daily living (ADL) in dementia-prevention trials of clinically normal individuals[114]. The ADL Prevention Instrument is a subjective self-report and informant-based scale consisting of 15 items. It has been shown to distinguish well between clinically normal individuals and those with preclinical AD and to be associated with future cognitive decline in cognitively normal individuals[115].

Participant versus study partner assessments

There exists an important complication in the tracking of early declines in preclinical AD using subjective scales: as an individual becomes more impaired and transitions from preclinical AD to MCI and then to AD dementia, that individual is less likely to provide a reliable self-report of his or her daily functioning, thus necessitating an informant report[116]. However, before MCI sets in, the individual with preclinical AD may be more attuned to early functional difficulties than an informant. Therefore, at different stages of AD, either self-report or informant-based subjective ADL scales might be more reliable, suggesting that both are required, at least in preclinical AD.

Prevention of preclinical AD

Therapeutic strategies in preclinical AD

Several lifestyle modifications are thought to possibly reduce the risk of developing dementia, including AD dementia[117]. Specifically, optimal management of hypertension[118] and treatment of hearing loss[119] as well as participating in regular aerobic exercise[120] are thought to contribute to risk reduction for AD dementia. Further work will be needed to evaluate these interventions in midlife and even earlier to assess for sustained long-term benefits. In addition, several therapeutics are targeting the various key biological elements in AD pathophysiological processes, namely, Aβ and tau (Tables 2 and 3).

Anti-Aβ approaches—For the past 2 decades, AD drug-development efforts have focused on disease modification and have been strongly influenced by the two key neuropathological hallmarks of AD: extracellular deposition of Aβ and the subsequent formation of intraneuronal neurofibrillary tangles. Therapeutic strategies aimed at preventing Aβ formation, lowering its soluble levels in the brain, blocking its aggregation into plaques and disassembling existing Aβ plaques are among the main approaches employed to slow the progression of AD. Key aspects of clinical trials for preclinical AD are the need for a long treatment period (3.5–4.5 years) given the slow rate of change in cognitive decline and the challenge of identifying individuals who are clinically asymptomatic yet harbor elevated brain Aβ.

Anti-Aβ approaches have been criticized as a mechanism of action since their initial development and testing. The number of negative trials over the past 20 years for mild to moderate AD and the limited efficacy observed in early AD trials have raised the question of whether Aβ is the right target or a sufficient target for disease-modifying treatments[121]. However, anti-Aβ approaches are the furthest along in development and represent the first class of disease-modifying therapeutics to be approved by the FDA. It is expected that earlier intervention in the AD continuum and combination therapies targeting other pathologies including tau, neuroinflammation and cerebrovascular disease will help to increase the likelihood of improved efficacy.

Aducanumab.—Aducanumab is an immunoglobulin (Ig)G1 monoclonal antibody that selectively binds to soluble and insoluble fibrillar Aβ aggregates[122]. It targets Aβ aggregates, including soluble oligomers and insoluble fibrils[123]. The phase 1b randomized trial PRIME showed significant reductions in the Aβ PET standard uptake value ratio composite score of aducanumab-treated patients, especially those treated with 10 mg per kg aducanumab at 54 weeks[124]. The brain Aβ burden decreased in a dose- and time-dependent manner in patients with prodromal or mild AD. Worsening on the CDR sum of boxes (CDR-SB) and Mini Mental State Examination scores was delayed by aducanumab treatment, indicating a positive effect on cognition and clinical progression[124]. Aducanumab is the first disease-modifying treatment for AD that has been approved by the FDA. It received an accelerated approval due to its dramatic effectiveness in removing Aβ plaque as indicated by Aβ PET, although the approval was mired in controversy. The accelerated approval pathway allows for clinical use of a drug with effects on a surrogate marker considered reasonably

likely to predict clinical benefit and requires additional post-approval studies to confirm clinical benefit. The EMERGE and ENGAGE trials were two phase 3, 18-month studies of early AD (prodromal and mild AD). However, both studies were terminated after an interim futility analysis demonstrated that one of the trials (ENGAGE) met futility criteria while the other (EMERGE) was trending positive[125]. However, while the data from the trials were extracted for futility analysis, participants continued in the studies at the sites for an additional 3 months before the studies were halted. In the larger dataset that included data collected during these 3 additional months, high-dose aducanumab in the EMERGE study showed benefits in the primary outcome, CDR-SB, slowing cognitive decline by 22% and in each of the other secondary outcomes, while low-dose aducanumab did not show benefits compared to placebo[125]. No benefits were seen for low-dose or high-dose aducanumab in the ENGAGE study in the larger dataset. In both the EMERGE and ENGAGE trials, Aβ PET imaging showed dose-related reductions in brain Aβ, indicating target engagement. Although they had identical designs, EMERGE and ENGAGE differed in the duration of exposure to high-dose aducanumab and the extent of fibrillar Aβ reduction in the brain. The total duration of exposure to high-dose aducanumab was higher in the positive EMERGE study and is thought to have accounted for the divergent outcomes. The FDA gave accelerated approval to aducanumab based on the surrogate endpoint of reduction of Aβ, which is the measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. The Centers for Medicare and Medicaid Services have declined coverage of aducanumab outside of approved clinical trials, and clinical use of the drug has been severely limited.

Gantenerumab.—Gantenerumab is also an IgG1 monoclonal antibody that binds with high affinity to aggregated Aβ species and removes Aβ plaques via Fcγ receptor-mediated microglial phagocytosis[126]. Gantenerumab neutralizes the neurotoxic effect of oligomeric $A\beta_{42}$ in vivo[126] and has been shown to reduce Aβ plaques[127]. Two pivotal phase 3 trials in patients with early AD, GRADUATE 1 (NCT03443973) and GRADUATE 2 (NCT03444870), with subcutaneously administered gantenerumab have been completed. Gantenerumab failed to meet its primary outcome in either study. Gantenerumab cleared only half as much plaque as expected, and fewer participants became Aβ negative as determined by PET scans than in previous trials. Clinical measures trended to improvement with an 8% slowing in cognitive decline. Participants who cleared Aβ below the positivity threshold did the best clinically[128]. Development of gantenerumab was halted, and a new formulation that uses transferrin transporter to help larger amounts of the antibody cross the blood–brain barrier is under development. Gantenerumab was also used in studies of autosomal dominant AD with negative results[129].

Donanemab.—Donanemab is an IgG1 that targets $A\beta_{p3–42}$, an N-terminal pyroglutamate Aβ epitope, present in Aβ plaques. This monoclonal antibody mechanism also reduces plaque through microglial-mediated phagocytosis[130]. A phase 1b trial showed a significant reduction in Aβ plaque that was observed even after a single dose[130], and a phase 2 result was positive for its primary cognitive–functional composite outcome[131]. The TRAILBLAZER-ALZ-2 (NCT04437511) phase 3 trial is determining the safety and

efficacy of donanemab in early AD, and the TRAILBLAZER-ALZ-3 study (NCT05026866) is being conducted in patients with preclinical AD.

Lecanemab.—Lecanemab is an Aβ-targeting monoclonal antibody with relative selectivity for the protofibrillar species of Aβ protein. The phase 2 trial of the antibody showed that it was well tolerated and demonstrated Aβ removal and reduction in cognitive decline, which was proportional to exposure[132]. The phase 3 trial of lecanemab in early AD has been completed (CLARITY AD). Topline results indicate that the trial was positive, showing a highly significant 27% slowing of clinical progression as measured by the CDR-SB, with consistent results on all key secondary outcomes[133]. The drug received accelerated approval and is expected to receive full approval in 2023. Additionally, lecanemab is being studied in preclinical AD as well as pre-preclinical AD, in which participants have intermediate elevation in brain Aβ[88].

An important adverse event to consider in the treatment of AD across its spectrum is that of amyloid-related imaging abnormalities (ARIA), which can be observed in two distinct presentations via MRI (ARIA-H and ARIA-E), following treatment with monoclonal antibodies that target Aβ plaques. ARIA-H refers to hemosiderin deposits presenting as microhemorrhages (hemorrhages < 10 mm) in the brain parenchyma and/or localized superficial siderosis (located in the subarachnoid space). ARIA-E refers to vasogenic edema in the brain parenchyma or sulcal effusions[134,135]. ARIA is believed to be driven by immune-mediated dissolution of Aβ aggregates in the cerebral blood vessels and brain parenchyma[136]. In the case of cerebrovascular Aβ deposits, it is thought to undermine the structural integrity of the blood vessel wall, leading to increased permeability and a localized hemorrhage or vasogenic edema. In most cases, ARIA-H and ARIA-E are asymptomatic, but, in severe cases, they can result in neurological symptoms such as headache, visual changes and death[137].

Solanezumab.—Solanezumab is a monoclonal antibody that selectively binds to soluble Aβ monomers to promote Aβ clearance. It slows further accumulation of Aβ but does not remove Aβ deposited in plaques. Solanezumab has also progressed through a large development program including two phase 3 trials that were completed in mild to moderate AD dementia. The phase 3 trials did not meet their primary endpoints[138,139]. Solanezumab was evaluated in the phase 3 randomized, placebo-controlled Anti-Amyloid in Asymptomatic Alzheimer's (A4) trial using a higher dose of solanezumab than that in the EXPEDITION trials and for a longer duration. Solanezumab did not slow cognitive decline on the primary outcome, the Preclinical Alzheimer Cognitive Composite, over 4.5 years in preclinical AD[140]. Overall, 36.1% of participants progressed to CDR Global Score (CDR-GS) > 0, which was similar between groups. Initial results suggest that the baseline Aβ level was the strongest predictor of cognitive decline. On Aβ PET imaging, Aβ continued to accumulate over time in both placebo and solanezumab groups, with less accumulation in the solanezumab group at the endpoint[140]. Additionally, the LEARN study, which enrolled participants with no elevation in brain Aβ, experienced no AD-associated cognitive decline over 8 years. These data suggest that more aggressive Aβ clearance is required even at the

preclinical stage of disease and further strengthen the notion that elevated brain Aβ levels lead to subsequent cognitive decline.

BACE inhibitors.—The discovery of β-site APP-cleaving enzyme 1 (BACE1) as the enzyme that initiates Aβ production and the identification of a mutation at the BACE1 cleavage site of APP that inhibited production of Aβ and was protective of AD[141,142] led to the development of several highly potent BACE inhibitors. However, their clinical trials failed to demonstrate efficacy, and most were associated with mild, self-limited, cognitive worsening[143-146].

Further evaluation of clinical trial data has raised the possibility that a low dose of BACE inhibition, which results in less-potent but still diminished Aβ production, similar to that observed with the protective mutation, that is, a mutation that reduces risk for AD, may provide a reasonable path forward for asymptomatic patients who do not have substantial plaque burden or associated symptoms[147].

Anti-tau approaches

Beyond Aβ as a target, the accumulation of tau aggregates in the brain is a key pathological hallmark of several neurodegenerative diseases, termed tauopathies, including AD. As transcellular spread of pathological tau aggregates has been implicated in disease progression, immunotherapy is being considered as a treatment for tauopathies. Given that tau lesions correlate better with the degree of dementia than do Aβ plaques, their clearance may also be clinically more efficacious once Aβ plaques develop and more proximal to when cognitive deficits become evident in AD. The most active mechanism of action is tau immunotherapy, with two active vaccines (AADvac1 and ACI-35) and six antibodies (LY3303560, RO7105705, BMS-986168, C2N-8E12, JNJ-63733657 and UCB0107) in clinical trials, although most of these therapies are still in the early stages of development and target stages later then preclinical AD[148]. The use of the ATN disease staging framework offers the potential for testing combination therapy with both anti-Aβ and anti-tau approaches, which may represent tailored interventions for AD across its various stages. Combining anti-Aβ and anti-tau therapies may provide additive or even synergistic benefits.

Current preclinical AD trials

We are now in an unprecedented era in AD therapeutic research. Phase 3 results from the aducanumab, gantenerumab, lecanemab and solanezumab trials and phase 2 results from the donanemab trials provide strong evidence that Aβ has a key role in AD-associated cognitive decline and that reducing brain amyloid is needed for efficacy. By the end of 2023, it is anticipated that there will be three FDA-approved anti-Aβ treatments for early AD. In addition, there are two large ongoing clinical trials, AHEAD and TRAILBLAZER-ALZ-3, in the preclinical AD stage. The AHEAD 3-45 trial (NCT04468659) is testing lecanemab in participants with preclinical AD as well as in individuals at an even earlier stage of AD, defined by an intermediate level of Aβ accumulation[88]. The SKYLINE trial (NCT05256134) was evaluating subcutaneous gantenerumab in preclinical AD until the negative readout of the GRADUATE 1 and GRADUATE 2 studies[128], further supporting

the notion that amyloid levels should be significantly reduced in order to achieve clinical efficacy. The TRAILBLAZER-ALZ-3 trial is testing donanemab in asymptomatic individuals between 65 and 80 years old who have evidence of elevated brain Aβ. The study will run for 3 years, with a clinical primary outcome of time to clinical progression as measured by the CDR-GS (NCT05026866). And, finally, prevention trials are ongoing or soon to begin in the populations with autosomal dominant AD or DS.

Recruitment challenges in preclinical AD

Recruitment challenges are especially demanding for trials in populations with preclinical AD, in which the minimal nature or absence of clinical symptoms means that individuals do not seek medical care for memory decline[149]. While AD dementia trials typically recruit from medical practices and clinics specializing in caring for patients with cognitive disorders, the population with preclinical AD requires a different approach that includes screening many cognitively normal individuals to fully enroll a prevention trial. Thus, trials for preclinical AD require a method to efficiently connect with individuals who are concerned about their risk for AD and prescreening those individuals who are at high risk. Moreover, clinical trials have historically lacked diversity with respect to under-represented racial groups about which there is limited information regarding efficacy of these new therapies and racial differences in biomarkers[150].

The Trial-Ready Cohort in Preclinical/prodromal AD (TRC-PAD) project has established a recruitment infrastructure for early-stage AD trials[151]. The initial outreach effort has enrolled about 52,000 participants who have consented online and enrolled in the Alzheimer Prevention Trials Webstudy (APT Webstudy). The Webstudy is an online tool designed to collect brief information on demographics, family history, medical history and subjective cognitive concerns. Unsupervised cognitive assessment collects data on intellectual and memory function relevant to possible early AD. Participants are asked to return to the website quarterly to provide longitudinal cognitive and subjective data. The APT Webstudy data are analyzed to determine the likelihood of elevation in brain Aβ levels; initial algorithms are based primarily on analysis of the pre-randomization data from the A4 trial[152]. Based on the risk determination, as well as proximity to active TRC-PAD clinical sites and the entry criteria for available trials, individuals may be invited for a blood draw at a nearby commercial laboratory for plasma AD biomarkers and then an in-person assessment and, based on the updated risk assessment, Aβ testing by Aβ PET or CSF. Those with Aβ results consistent with AD are invited to be cohort participants, are followed in-person longitudinally and are ready for enrollment into trials. Those without Aβ abnormalities continue to be followed remotely in the APT Webstudy to continue to provide data for updated risk assessments.

Future directions: population screening and primary prevention

Two major recent developments in AD therapeutic research, the demonstration that effective targeting of Aβ slows clinical progression and the validation of highly accurate plasma biomarkers of AD neurobiology[86], indicate the way forward toward primary prevention of the disease.

While there has been compelling evidence, particularly from genetic considerations, that Aβ accumulation drives AD, it has now been proven that reducing fibrillar Aβ in the brain is clinically beneficial at the early symptomatic stage of the disease. It is reasonable to be optimistic that intervention at the presymptomatic stage, when there is less irreversible neurodegeneration, will yield more than the 27% slowing shown with lecanemab in early AD. The results of the preclinical AD trials will arrive later in the decade.

We can now envision primary prevention of AD. The new plasma assays of Aβ ratios and p-tau species demonstrate abnormalities before measurable fibrillar Aβ accumulation as measured by PET scanning. As this technology continues to improve, we will be able to monitor the general population, perhaps starting around the age of 50 years, for evidence of Aβ dysregulation pointing to eventual brain accumulation. Routine longitudinal monitoring of plasma biomarkers may allow identification of those likely to accumulate Aβ. Candidate primary prevention therapies include low-dose BACE inhibitors, γ-secretase modulators and active anti-Aβ vaccination. Because Aβ is essential to the initiation of the AD neuropathological cascade, we anticipate that accurate monitoring and effective intervention against Aβ dysregulation will have a major impact on the incidence of AD, even greater than the impact of statin therapy on cardiovascular disease. Much work remains to be done to optimize and validate plasma assays for this purpose and demonstrate the safety and efficacy of preventive therapies; implementation of this approach to primary prevention is at least a decade away. The pathway forward is taking shape.

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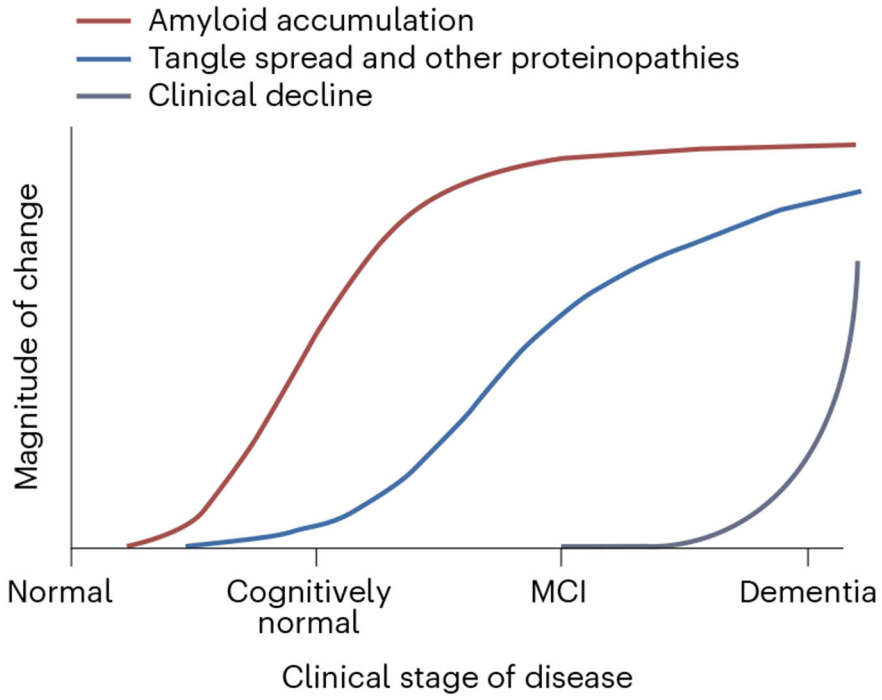

Fig. 1 |. Continuum of Alzheimer's disease over 25 years.
Neuropathological changes in Alzheimer's disease occur decades before the manifestation of clinical symptoms. MCI, mild cognitive impairment.

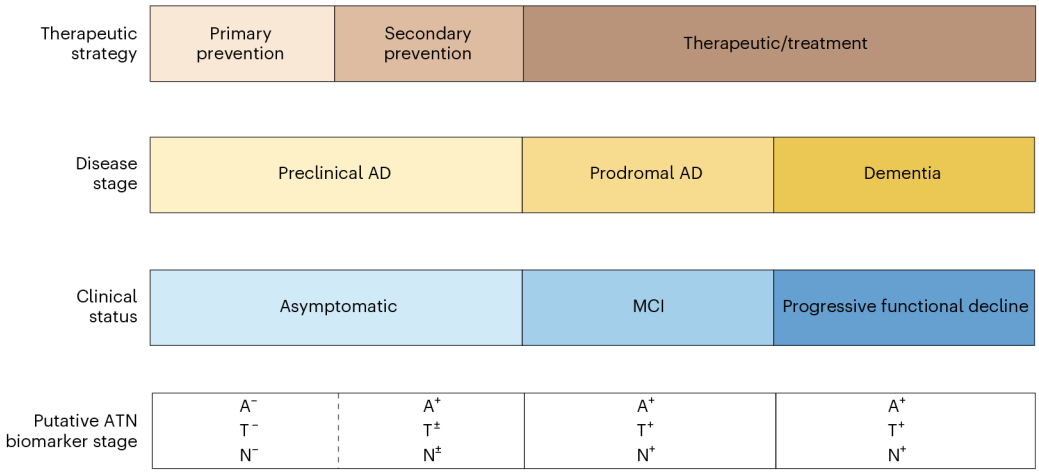

Fig. 2 |. Biomarkers and the amyloid, tau and neurodegeneration (ATN) classification. Biomarkers can be used for individualized risk profiling and neuropathological staging of patients along the Alzheimer's disease (AD) continuum. MCI, mild cognitive impairment.

Table 1 |

Amyloid, tau and neurodegeneration (ATN) classification

AT(N) profiles	Biomarker category	Part of Alzheimer's disease (AD) continuum (yes or no)	Stable cognition	MCI	Dementia
$A^-T^-N^-$	Normal biomarkers	No	Stable cognition + normal AD biomarkers	MCI + normal AD biomarkers	Dementia + normal AD biomarkers
$A^+T^-N^-$	AD pathological change	Yes	Preclinical AD pathological change	MCI + AD pathological change	Dementia + AD pathological change
$A^+T^+N^-$	AD	Yes	Preclinical AD	Prodromal AD	AD + dementia
$A^+T^+N^+$	AD	Yes	Preclinical AD	Prodromal AD	AD + dementia
$A^+T^-N^+$	AD and concomitant suspected non-AD pathological change	Yes	Preclinical AD	Prodromal AD	AD + dementia
$A^-T^+N^-$	Non-AD pathological change	No	Preclinical non-AD	MCI not due to AD	Non-AD dementia
$A^-T^-N^+$	Non-AD pathological change	No	Preclinical non-AD	MCI not due to AD	Non-AD dementia
$A^-T^+N^+$	Non-AD pathological change	No	Preclinical non-AD	MCI not due to AD	Non-AD dementia

MCI, mild cognitive impairment.

Table 2 |

Disease-modifying agents targeting amyloid-β (Aβ)

Target/mechanism	Drug	Study population	Clinical trial identifier
BACE1 inhibitor (β-secretase inhibitor)	Verubecestat	Mild to moderate AD	NCT01739348
		Prodromal AD	NCT01953601
	Lanabecestat	Prodromal AD; mild AD	NCT02245737, NCT02783573
	Atabecestat	Preclinical AD	NCT02569398
	Umibecestat	Preclinical AD	NCT03131453, NCT02565511
	Elenbecestat	Prodromal to mild AD	NCT02956486, NCT03036280
γ-Secretase inhibitor	Semagacestat	Mild to moderate AD	NCT01035138, NCT00762411, NCT00594568
	Avagacestat	Prodromal AD	NCT00890890
γ-Secretase modulator	Tarenflurbil	Mild AD	NCT00105547
Inhibitors of Aβ aggregation	Scyllo-inositol	Mild to moderate AD	NCT00568776
		DS	NCT01791725
	Tramiprosate	Mild to moderate AD	NCT00088673
	Valiltramiprosate	APOE4/4 early AD	NCT04770220
Active immunotherapy (anti-Aβ vaccine)	AN-1792	Mild to moderate AD	NCT00021723
	ACI.24	DS	NCT02738450
	ACI24.060	Prodromal AD and DS	NCT05462106
	Amilomotide (CAD106)	Preclinical AD	NCT02565511
	Vanutide cridificar (ACC-001)	Mild to moderate AD	NCT00955409, NCT00960531, NCT01238991
			NCT01284387
	ABvac40	Prodromal AD	NCT03461276
	Lu AF20513	Mild AD; prodromal to mild AD	NCT02388152, NCT03819699, NCT03668405
	UB-311	Mild AD	NCT02551809
			NCT03531710
Passive immunotherapy (anti-Aβ antibody)	Bapineuzumab (AAB-001)	Mild to moderate AD	NCT00575055, NCT00574132
	Solanezumab (LY2062430)	Mild to moderate AD; mild AD, preclinical AD	NCT00905372, NCT00904683, NCT01900665
			NCT02008357
	Crenezumab (RG7412)	Prodromal to mild AD	NCT02670083, NCT03114657

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Target/mechanism	Drug	Study population	Clinical trial identifier
	Gantenerumab (RO4909832)	Prodromal to mild AD	NCT03443973, NCT03444870
	Aducanumab (BIIB037)	Prodromal to mild AD	NCT02477800, NCT02484547
	BAN2401	Prodromal to mild AD	NCT03887455
		Preclinical AD; pre-preclinical AD	NCT04468659

AD, Alzheimer's disease; DS, Down syndrome.

Table 3 |

Anti-tau therapies

Mechanism	Drug	Population	Clinical trial identifier
Active immunotherapy (anti-tau vaccine)	AADvac1	Mild AD	NCT02579252
	ACI-35	Mild to moderate AD	NCT04445831
Passive immunotherapy (anti-tau antibody)	Gosuranemab (BIIB092/BMS-986168)	Prodromal to mild AD	NCT03352557
	Tilavonemab (ABBV-8E12/C2N-8E12)	Prodromal to mild AD	NCT02880956
Passive immunotherapy (anti-tau antibody)	Semorinemab (RO7105705)	Prodromal to mild AD; moderate AD	NCT03289143, NCT03828747
	Zagotenemab (LY3303560)	Prodromal to mild AD	NCT03518073

AD, Alzheimer's disease.