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REVIEW

What works and what does not work in Alzheimer's disease? From interventions on risk factors to anti-amyloid trials

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with no approved disease-modifying therapy (DMT). In this review, we summarize the various past approaches taken in an attempt to find treatments capable of altering the long-term course for individuals with AD, including: translating epidemiological observations into potential treatment options; seeking a single-treatment approach across the continuum of AD severity; utilizing biomarkers for assessing target engagement; using biomarkers as early surrogates of clinical efficacy; and enriching study populations to demonstrate adequate placebo decline during the limited duration of clinical trials. Although targeting the amyloid-β (Aβ) pathway has been central to the search for an effective DMT, to date, trials of anti-Aβ monoclonal antibodies have failed to consistently demonstrate significant clinical efficacy. Key learnings from these anti-Aβ trials, as well as the trials that came before them, have shifted the focus within clinical development programs to identifying target populations thought most likely to benefit from treatments (i.e., individuals at an earlier stage of disease). Other learnings include strategies to increase the likelihood of showing measurable improvements within the clinical trial setting by better predicting decline in placebo participants, as well as developing measures to quantify the needed treatment exposure (e.g., higher doses). Given the complexity associated with AD pathology and progression, treatments targeting non-amyloid AD pathologies in combination with anti-amyloid therapies may offer an alternative for the successful development of DMTs.

KEYWORDS

Alzheimer's disease, anti-Aβ monoclonal antibodies, biomarkers, clinical trials, disease-modifying therapy

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale—Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS-(i)ADL, Alzheimer's Disease Cooperative Study—Activities of Daily Living (instrumental subscale); ADCS-ADL, Alzheimer's Disease Cooperative Study—Activities of Daily Living; Aβ, amyloid-β; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; BACE, β-secretase; CAIDE, Cardiovascular Risk Factors, Aging, and Incidence of Dementia; CANTAB, Cambridge Neuropsychological Test Automated Battery; CDR-SB, Clinical Dementia Rating—Sum of Boxes; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CNS, central nervous system; CSF, cerebrospinal fluid; DAD, Disability Assessment for Dementia; DIAN-TU, Dominantly Inherited Alzheimer Network Trials Unit; DMT, disease-modifying therapy; FAST, Functional Assessment Staging Test; FCSRT, Free and Cued Selective Reminding Test; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; IgG1, immunoglobulin G1; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; NTB, Neuropsychological Test Battery; PET, positron emission tomography; pTau, phosphorylated tau; PSEN1, presenilin-1; RR, relative risk; SD, standard deviation; SUVR, standardized uptake value ratio; tTau, total tau.

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with a complex underlying pathology (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011). The progression of AD occurs along a continuum, beginning with asymptomatic neuropathological changes that gradually lead to memory loss as well as other cognitive, functional, and behavioral impairments (Burns & Iliffe, 2009; Rafii & Aisen, 2015). These impairments result in the gradual loss of independence, with many patients eventually becoming unable to perform routine activities of daily living and, ultimately, may lead to premature death (Apostolova, 2016). Globally, the economic cost of dementia was estimated to be $818 billion in 2015, a 35.4% increase in cost compared with the $604 billion estimate from 2010 (Wimo et al., 2017).

Despite the devastating consequences and the overall burden of AD, an effective disease-modifying therapy (DMT) capable of stopping or slowing the progression of the clinical symptoms and the underlying pathology, has not been established for this disease. Current therapies available in clinical practice are limited to symptomatic treatment and do not specifically slow underlying neuronal damage or, therefore, alter the course of disease progression (Grossberg, Tong, Burke, & Tariot, 2019; Yiannopoulou & Papageorgiou, 2013). In this article, we aim to review some of the approaches tried, as well as lessons learned, in the search for a DMT capable of effectively stopping or slowing the decline of individuals with AD. The specific approaches that we focus on include: (1) translating epidemiological observations into potential treatment options; (2) seeking a single-treatment approach across the continuum of AD severity; (3) utilizing biomarkers for assessing target engagement; (4) using biomarkers as early surrogates of clinical efficacy; and (5) enriching study populations to demonstrate adequate placebo decline during the limited duration of clinical trials.

2 | TRANSLATING EPIDEMIOLOGICAL OBSERVATIONS INTO POTENTIAL TREATMENT OPTIONS

Many risk factors, both modifiable and non-modifiable, for neurodegeneration and associated cognitive decline have already been identified (Figure 1). Risk factors like causal genetic mutations (e.g., presenilin-1 [PSEN1] mutation among others) (Kelleher & Shen, 2017; Naj & Schellenberg, 2017), genetic risk factors (e.g., the presence of the ε4 allele of apolipoprotein E [*APOE*] gene) (Liu, Liu, Kanekiyo, Xu, & Bu, 2013), and aging (Nieoullon, 2011) are non-modifiable. Other risk factors, however, are potentially modifiable and include education (Barnes & Yaffe, 2011), environmental factors (Nieoullon, 2011), psychosocial factors (Barnes & Yaffe, 2011; Nieoullon, 2011), menopause/low estrogen levels (Pike, 2017), metabolic/cardiovascular risk factors (Barnes & Yaffe, 2011; Christensen & Pike, 2015; Kivipelto & Solomon, 2006; Smith et al., 2018; Sommer et al., 2017), and health behaviors/lifestyle factors (Barnes & Yaffe, 2011). The relative risk (RR) of developing AD attributable to potentially modifiable risk factors has been summarized by Barnes & Yaffe (Barnes & Yaffe, 2011) and is reported in Figure 2. While applying epidemiological observations based on modifiable or non-modifiable risk factors may offer potential treatment options that help to provide a personalized approach to treating patients with AD, in this section we primarily focus on non-pharmacological interventions for potentially modifiable risk factors.

The approach of targeting individual, potentially modifiable risk factors in individuals with AD dementia has been evaluated in interventional studies (Table 1). However, it is important to keep in mind that an observed association with AD does not necessarily equate to causality, which may explain in part why the majority of these interventions have failed to demonstrate a significant effect on disease progression so far. For example, modifying metabolic/cardiovascular risk factors did not lead to a significant slowing of cognitive decline (AD2000 Collaborative Group, 2008; Aisen et al., 2000, 2003, 2008; Feldman et al., 2010; Gold et al., 2010; Harrington et al., 2011; Kwok et al., 2011; Reines et al., 2004; van Rossum et al., 2012; Sano et al., 2011; SPRINT MIND Investigators for the SPRINT Research Group et al., 2019; Stein, Scherer, Ladd, & Harrison, 2011; Sun, Lu, Chien, Chen, & Chen, 2007; Van Gool, Weinstein, Scheltens, & Walstra, 2001); similar results were observed with estrogen replacement therapy (Table 1) (Mulnard et al., 2000; Rigaud et al., 2003). In addition, there is evidence that supports the notion that regular physical exercise may serve as an option for preventing cognitive decline and dementia. Although some observational studies have demonstrated robust associations of physical activity with both delayed onset (Larson et al., 2006) and a reduced risk of dementia

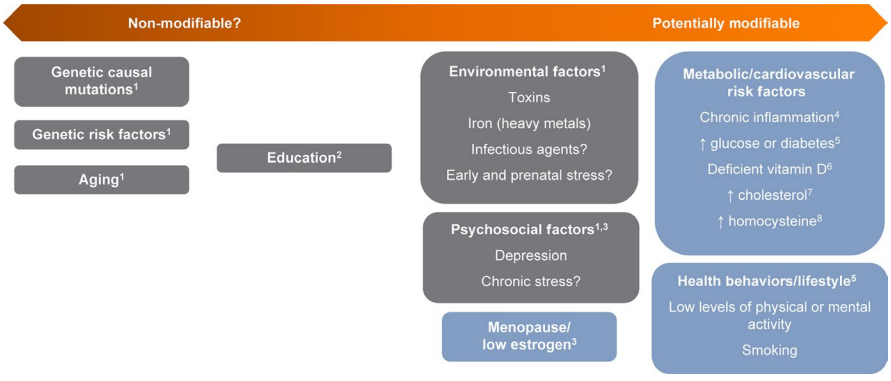

FIGURE 1 Important risk factors for neurodegeneration. References: 1. (Nieoullon, 2011). 2. (McKenzie et al., 2017). 3. (Pike, 2017). 4. (Christensen & Pike, 2015). 5. (Barnes & Yaffe, 2011). 6. (Sommer et al., 2017). 7. (Kivipelto & Solomon, 2006). 8. (Smith et al., 2018)

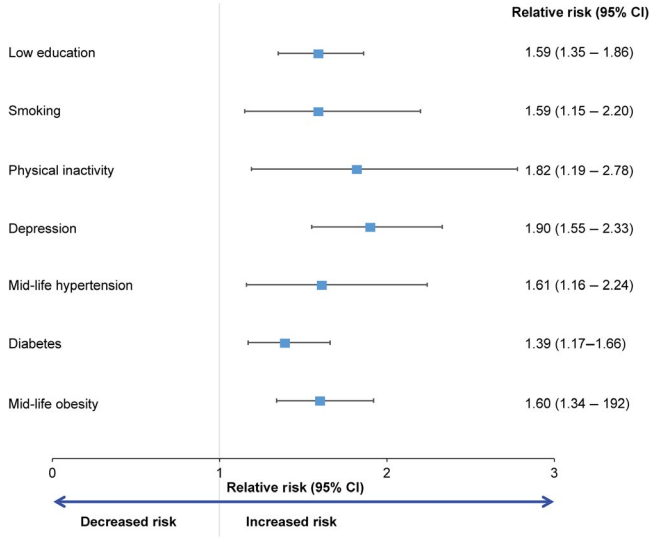

FIGURE 2 Relative risk of modifiable risk factors in Alzheimer's disease. Reference: (Barnes & Yaffe, 2011)

(Andel et al., 2008; Buchman et al., 2012; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001), other observational studies have failed to show an effect on cognitive performance (Makizako et al., 2015; Smith et al., 2011). For trials evaluating the efficacy of exercise intervention programs, methodological heterogeneity across studies may have an influence on whether a benefit is observed and can also limit the conclusions that are drawn from the analyses (Farina, Rusted, & Tabet, 2014). While observational studies have inherent limitations that are difficult to overcome, they can inform interventional studies and remain a key area of AD research (Haeger, Costa, Schulz, & Reetz, 2019).

One reason for the lack of success associated with interventional studies that targeted potentially modifiable risk factors may be the presence of unaccounted confounding factors (Andrews, Marcora, & Goate, 2019). Thus, targeting a potentially modifiable risk factor without controlling for all potential confounders could render the interventional study more likely to be unsuccessful. Furthermore, the type of intervention may significantly influence clinical efficacy. For example, exercise interventions vary greatly in their methodology; some may include aerobic or resistance exercises exclusively, whereas others combine exercise interventions with cognitive stimulation or with nutritional supplements (Farina et al., 2014; Haeger et al., 2019), resulting in a differential effect on cognition. In addition, the duration of the intervention itself, regardless of the approach, may also limit our ability to detect clinical efficacy; intervention durations even > 1 year (Aisen et al., 2008; Feldman et al., 2010; Sano et al., 2011; Van Gool et al., 2001) may not provide an adequate exposure time to result in a measurable clinical benefit. Lastly, some interventions may be more efficacious in earlier stages of AD but are introduced or evaluated in later stages of the disease course, such as during mild-to-moderate AD (AD2000 Collaborative Group, 2008; Aisen et al., 2003, 2008; Feldman et al., 2010; Gold et al., 2010; Harrington et al., 2011; Kwok et al., 2011; Mulnard et al., 2000; Reines et al., 2004; Sano et al., 2011; Stein et al., 2011; Sun et al., 2007) or in individuals with varying levels of dementia severity (Farina et al., 2014).

Although targeting individual risk factors has not yielded clear success for individuals already symptomatic with AD, epidemiological evidence suggests that a multidomain approach may benefit individuals at risk for AD (Ngandu et al., 2015). This concept was examined in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (ClinicalTrials.gov, 2016 [NCT01041989]; Ngandu et al., 2015). The FINGER study was a 2-year, randomized controlled multidomain interventional study to prevent cognitive decline in at-risk elderly people from the general population. The study enrolled 1,260 participants, who were recruited from population-based national surveys. Participants were aged 60–77 years, with Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) Risk Score ≥ 6 and cognition measures that were at mean or slightly lower than expected for age evidenced by their performance during Consortium to Establish a Registry for Alzheimer's Disease screening. Eligible participants were randomized to either a multidomain intervention group (n = 631), which included nutritional counseling, physical activity, cognitive training, and vascular risk factor monitoring; or to a control group (n = 629) that received general health advice. Findings on the primary outcome, assessed by the Neuropsychological Test Battery (NTB), showed a between-group difference favoring the intervention group, which had a 25% greater improvement in the NTB total score at 24 months compared with control treatment (Ngandu et al., 2015).

Analyses of the NTB domain scores demonstrated improvement in executive functioning (83% higher) and processing speed (150% higher) in the intervention versus control groups (Ngandu et al., 2015). Moreover, health-related quality of life declined in the control group, but improved in the intervention group; general health and physical function at both 12 and 24 months were statistically significantly better in the intervention group (Strandberg et al., 2017). Overall, these results suggest that intervention based on epidemiological observations can lead to a viable multidomain interventional strategy for preserving aspects of cognition in identified at-risk individuals (Ngandu et al., 2015; Strandberg et al., 2017). However, they do not show that such benefits translate into a reduced risk for all-cause dementia, or dementia because of AD.

There are other multidomain interventional studies in individuals with cognitive impairment or AD that have been completed (Nousia et al., 2018; Rolland, Barreto, Maltais, Guyonnet, Cantet, Andrieu, & Vellas, 2019; Vellas et al., 2014) or are ongoing (ClinicalTrials.gov, 2019h [NCT03657745]; ClinicalTrials.gov, 2019i [NCT04095962]; Yaffe et al., 2019). The analysis of the FINGER 7-year extended follow-up is underway, and these additional data along with other larger multidomain intervention studies being implemented across the globe will advance our understanding of multidomain interventions (ClinicalTrials.gov, 2016 [NCT01041989]; Kivipelto, Mangialasche, & Ngandu, 2018; Rosenberg, Mangialasche, Ngandu, Solomon, & Kivipelto, 2020).

TABLE 1 Interventions targeting potentially modifiable risk factors in individuals with AD

Failed Agents		Results Summary
NSAIDs and other anti-inflammatory agents	Rofecoxib	No significant difference on ADAS-Cog[a] or CDR-SB versus placebo at 1 year in mild-to-moderate AD (Aisen et al., 2003; Reines et al., 2004)
	Naproxen	No significant difference on ADAS-Cog[a] or CDR-SB versus placebo at 1 year in mild-to-moderate AD (Aisen et al., 2003)
	Prednisone	No difference on ADAS-Cog[a] or CDR-SB versus placebo at 1 year in probable AD (Aisen et al., 2000)
	Hydroxychloroquine	No difference on ADAS-Cog[a] versus placebo at 18 months in early AD (minimal or mild AD) (Van Gool et al., 2001)
	Aspirin	Higher mean MMSE and lower mean basic ADLS score versus no aspirin at 3 years in mild-to-moderate AD (AD2000 Collaborative Group, 2008)
Estrogen replacement therapy	Estrogen	No improvement on Clinical Global Impression of Change (CGIC), MMSE, or CDR at 1-year in mild-to-moderate AD (Mulnard et al., 2000) No significant changes on ADAS-Cog, MMSE, or CGC-plus versus placebo at 28 weeks in mild-to-moderately severe AD (Rigaud et al., 2003)
Insulin control	Rosiglitazone	No difference on ADAS-Cog[a] versus placebo at week 24 in mild-to-moderate probable AD (Gold et al., 2010) No difference on ADAS-Cog[a] or CDR-SB at week 48 in mild-to-moderate AD (Harrington et al., 2011)
Vitamin D	Vitamin D Supplementation	No benefit on ADAS-Cog[a] versus low-dose vitamin D in mild-to-moderate AD (Stein et al., 2011)
Statins	Simvastatin	No effect on ADAS-Cog[a] versus placebo at 18 months in mild-to-moderate AD (Sano et al., 2011)
	Atorvastatin	No significant difference on ADAS-Cog11 or ADCS-CGIC versus placebo at week 72 in mild-to-moderate probable AD (Feldman et al., 2010)
Homocysteine	B_6 + B_{12} + Folic Acid	No significant difference on ADAS-Cog11 or ADL function versus placebo at week 26 in mild-to-moderate AD (Sun et al., 2007) No beneficial effect on ADAS-Cog[a] or CDR-SB over 18 months versus placebo in mild-to-moderate AD (Aisen et al., 2008)
	Methylcobalamin + Folic Acid	No significant difference on Mattis dementia rating scale (MDRS) at 24 months in mild-to-moderate AD (Kwok et al., 2011)

[a]Performed per Rosen *et al.* (Rosen, Mohs, & Davis, 1984).

To summarize, addressing even strong risk factors for the development of AD in individuals who are already symptomatic has not been beneficial to date. The current multimodal interventions for elderly persons at risk for AD have demonstrated an impact on the type of age-associated cognitive decline observed with normal aging in the absence of dementia, but they have yet to prove an effect relevant to AD or other forms of dementia.

3 | SEEKING A SINGLE-TREATMENT APPROACH ACROSS THE CONTINUUM OF AD SEVERITY

AD progression occurs along a continuum, beginning as an asymptomatic preclinical stage and eventually resulting in cognitive and functional impairments as well as, ultimately, premature mortality (Apostolova, 2016). Based on this continuum, is it feasible for a drug to demonstrate efficacy during all stages of the disease? Early investigations using primarily neurotransmitter-based therapies have suggested that it is not. In Table 2, we have summarized the effect sizes of some AD drug therapies that have been evaluated to date.

Currently, the only approved therapeutic options are symptomatic treatments such as the *N*-methyl-D-aspartate receptor antagonist, memantine, and acetylcholinesterase inhibitors; both therapies have demonstrated temporary slowing of cognitive decline alone or in combination compared with placebo (Howard et al., 2012; Parsons, Danysz, Dekundy, & Pulte, 2013; Raina et al., 2008). Interestingly, memantine has shown a greater effect size on cognition and functional measures in more severe stages of AD (Schneider, Dagerman, Higgins, & McShane, 2011; Winblad, Jones, Wirth, Stoffler, & Möbius, 2007), whereas cholinesterase inhibitors have shown efficacy in a broader population, including individuals with mild, moderate, and severe AD (Table 2) (Blanco-Silvente et al., 2017; Winblad et al., 2009). In addition to their use as monotherapies, the combined use of memantine and acetylcholinesterase inhibitors has been shown to reduce clinical worsening in moderate-to-severe AD compared with those receiving the cholinesterase inhibitor, donepezil, alone (Atri et al., 2013), although this additive effect was no longer statistically significant compared with placebo following 1 year of treatment in a different study with

TABLE 2 Effect sizes of different classes of AD therapies

Therapy	Outcome measure	Prodromal AD	Mild AD	Moderate AD	Severe AD
Memantine[1,2]	Cognition[a]	NE	−0.17 (−1.60, 1.26)	−0.26 (−0.37, −0.16)	
	Function[b]	NE	0.62 (−1.64, 2.71)	−0.18 (−0.28, −0.08)	
Cholinesterase inhibitors[3–5]	Cognition[c]	−0.07 (−0.16, 0.01)	0.38[d](0.28, 0.47)[d]		0.51[e](p < .0001)[e]
	Function[b]	0.30 (−0.26, 0.86)	0.16 (0.11, 0.20)		0.17[d](p = .03)[d]
Anti-amyloid antibodies[6–9]	Cognition[f] Solanezumab[6]	?	0.07[g]		NE
	Bapineuzumab[7]	NE	0.14[h](−0.72, 0.99)[h]		NE
	Aducanumab[8]	−0.27 (p = .010)[i]		NE	NE
		−0.12 (p = .0245)[j]			
	Crenezumab[9]	0.10 (−2.15, 2.35)[k]		ND	NE
	Function[l] Solanezumab[6]	?	0.11[f]		NE
	Bapineuzumab[7]	NE	1.35[g] (−1.74, 4.43)[g]		NE
	Aducanumab[8]	−0.40 (p = .001)[i]		NE	NE
		−0.18 (p = .152)[j]			
	Crenezumab[9]	1.34 (−2.30, 4.98)[j,k]		ND	NE

Note: Effects sizes are Cohen's d unless indicated. The shading used in the outcome measure results for prodromal AD, mild AD, moderate AD, and severe AD represent the following: red, non-significant; green, significant or trend toward significance; yellow, unknown (trial ongoing).

NE; not evaluated; ND; not determined.

References: 1. (Schneider et al., 2011). 2. (Winblad et al., 2007). 3. (Tricco et al., 2013). 4. (Blanco-Silvente et al., 2017). 5. (Winblad et al., 2009). 6. (Gold, 2017). 7. (Abushouk et al., 2017). 8. (Biogen, 2019). 9. F. Hoffmann-La Roche Ltd; data on file.

[a]Cognition was assessed using the Alzheimer Disease Assessment Scale–cognitive subscale (ADAS-Cog) for mild AD and the ADAS-cog and Severe Impairment Battery (SIB) for moderate and severe AD.

[b]Function was assessed using the Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS-ADL) scale (19- or 23-item scale for moderate to severe AD; number of items not specified for mild AD ADCS-ADL scale).

[c]Cognition was assessed using ADAS-cog for prodromal, ADAS-cog or the Mini-Mental State Examination (MMSE) for mild and moderate AD, and using SIB for severe AD.

[d]Results showed a trend toward significance.

[e]Donepezil only; confidence interval around effect size not reported but did not include zero.

[f]Cognition was assessed using ADAS-Cog-14 for solanezumab, ADAS-Cog-11 for bapineuzumab. ADAS-Cog13 for aducanumab and crenezumab.

[g]Confidence interval not reported.

[h]Reported as standardized mean difference.

[i]EMERGE (ClinicalTrials.gov 2019m [NCT02484547]) ITT population (high-dose aducanumab); confidence interval not reported.

[j]ENGAGE (ClinicalTrials.gov, 2019q [NCT02477800]) ITT population (high-dose aducanumab); confidence interval not reported.

[k]Difference reported as placebo minus crenezumab.

[l]Function was assessed using the Disability Assessment for Dementia scale for bapineuzumab, and ADCS-ADL for solanezumab, aducanumab (Mild Cognitive Impairment version), and crenezumab.

different methodology and outcome measures (Howard et al., 2012). Furthermore, discontinuation of cholinesterase inhibitors in patients with AD or non-AD dementia has been associated with behavioral worsening (Daiello et al., 2009), suggesting these agents may also help stabilize behavioral issues. While these agents have demonstrated efficacy in treating the symptoms of AD (Grossberg et al., 2019; Yiannopoulou & Papageorgiou, 2013), finding an efficacious DMT that can effectively slow or prevent the progression of AD remains a high unmet needed.

In recent years, most DMTs in development have targeted the amyloid-β (Aβ) pathway, one of the main pathological hallmarks of AD. According to the amyloid hypothesis, accumulation of pathological Aβ species results in neurodegeneration, which eventually leads to clinical symptoms such as cognitive and functional impairments (Hardy & Selkoe, 2002; Masters et al., 2015; Selkoe & Hardy, 2016). Anti-Aβ monoclonal antibodies, including bapineuzumab (Rinne et al., 2010; Salloway et al., 2009, 2014), solanezumab (Doody et al., 2014; Farlow et al., 2012; Honig et al., 2018; Siemers et al., 2010), aducanumab (Biogen, 2019; ClinicalTrials.gov, 2019q [NCT02477800]; Sevigny et al., 2016; ClinicalTrials.gov 2019m [NCT02484547]), crenezumab (Cummings, Cohen, et al., 2018; Salloway et al., 2018; ClinicalTrials.gov, 2019p [NCT02670083]; ClinicalTrials.gov, 2019o [NCT03114657]), and ponezumab (Landen et al., 2017), have been tested previously in participants

with sporadic AD (van Dyck, 2018), while clinical trials evaluating gantenerumab (Ostrowitzki et al., 2017; ClinicalTrials.gov, 2019n [NCT03444870]; ClinicalTrials.gov, 2019f [NCT03443973]), donanemab (ClinicalTrials.gov, 2019l [NCT03367403]), and BAN2401 (ClinicalTrials.gov, 2019k [NCT03887455]) are still ongoing. Although previous clinical trials that tested anti-Aβ monoclonal antibody therapies in various stages of AD failed to demonstrate a statistically significant impact on cognitive decline, the results from the phase Ib trial of aducanumab, PRIME, demonstrated reduced brain Aβ and slowing of clinical decline (Sevigny et al., 2016; Sevigny, Chiao, Williams, Miao, & O'Gorman, 2015). A more recent analysis of aducanumab phase III study results may have changed the landscape in AD once again, suggesting that targeting the amyloid pathology in early (prodromal-to-mild) AD could still be a viable strategy (Biogen, 2019). Moreover, each trial evaluating the efficacy of anti-Aβ monoclonal antibodies has produced key learnings that have helped inform the development of clinical programs and revealed the impact that stage of progression along the AD continuum may have on the success of a therapy; we summarize some of these results in the following section.

Bapineuzumab, a fully humanized immunoglobulin G1 (IgG1) N-terminal-specific anti-Aβ monoclonal antibody (Kerchner & Boxer, 2010; Salloway et al., 2014), was evaluated in several phase II and III studies investigating efficacy on clinical and biomarker outcome measures in participants with mild-to-moderate AD (Blennow et al., 2012; Brody et al., 2016; Rinne et al., 2010; Salloway et al., 2009, 2014). Unfortunately, these studies did not demonstrate a significant difference in clinical outcome measures (e.g., Alzheimer's Disease Assessment Scale—Cognitive Subscale 11 [ADAS-Cog11], Disability Assessment for Dementia [DAD] scale, and Mini-Mental State Examination [MMSE]) in participants treated with bapineuzumab versus placebo (Salloway et al., 2014).

During phase III testing of solanezumab, a humanized IgG1 anti-Aβ monoclonal antibody that binds to the mid-domain of the Aβ peptide (van Dyck, 2018), pre-specified analyses of the EXPEDITION 1 trial data in individuals with mild versus moderate AD indicated a potential for greater efficacy in a milder/earlier disease stage population. This observation led to a change in the primary cognitive outcome measure in EXPEDITION 2 from ADAS-Cog11 to ADAS-Cog14 in participants with mild AD (Doody et al., 2014). Furthermore, the pre-specified pooled secondary analyses of the EXPEDITION 1 and EXPEDITION 2 results also demonstrated that participants with mild AD treated with solanezumab had slower cognitive decline versus the placebo group, as measured by ADAS-Cog14, ADAS-Cog11, MMSE, and the Alzheimer's Disease Cooperative Study—Activities of Daily Living instrumental subscale (ADCS-iADL) scores ($p < .05$ for each efficacy outcome measure) (Siemers et al., 2016). Results of these secondary analyses served as the basis for EXPEDITION 3, a phase III placebo-controlled, double-blind study in participants with mild AD who were amyloid-positive by florbetapir positron emission tomography (PET) or by CSF Aβ(1–42) measurements (Honig et al., 2018). Unfortunately, even in the selected population with mild AD, solanezumab showed no slowing of cognitive decline on the primary outcome measure of ADAS-Cog14 (Honig et al., 2018). Since the primary outcome in the EXPEDITION 3 trial did not reach significance, analyses of the secondary outcome measures were descriptive. Although participants in both groups showed worsening via the MMSE and Clinical Dementia Rating—Sum of Boxes (CDR-SB), results favored treatment with solanezumab (MMSE mean [standard deviation (*SD*)] change, −3.17 [0.15]; CDR-SB mean [*SD*] change, 1.87 [0.10]) versus placebo (MMSE mean [*SD*] change, −3.66 [0.16]; CDR-SB mean [*SD*] change, 2.21 [0.11]) (Honig et al., 2018). A possible explanation for the lack of efficacy was attributed to ineffective dosing; the penetration of the 400 mg dose of solanezumab into the central nervous system was only 0.1%–0.3% of the plasma concentration and may have been too low to result in clinical efficacy (Honig et al., 2018). Thus, dose escalation has been implemented in the secondary prevention trials investigating earlier intervention of solanezumab in individuals who may be at risk for memory loss because of AD (Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease [A4] trial) (ClinicalTrials.gov, 2018 [NCT02008357]) and in individuals at risk for or with dominantly inherited AD in the Dominantly Inherited Alzheimer Network Trials Unit [DIAN-TU] (ClinicalTrials.gov, 2019j [NCT01760005]). The dose of solanezumab has been quadrupled in both the A4 (Aisen et al., 2018; Panza et al., 2018), and the DIAN-TU trials (ClinicalTrials.gov, 2019j [NCT01760005]; DIAN Trials Unit and Washington University School of Medicine in St. Louis, 2019).

Aducanumab is another fully human IgG1 anti-Aβ monoclonal antibody with selective affinity for the N-terminus of Aβ aggregates (van Dyck, 2018). The double-blind phase Ib study of aducanumab, PRIME, demonstrated a slowing of clinical decline in individuals with prodromal or mild AD, as measured by CDR-SB and MMSE (Sevigny et al., 2016). These results suggested that aducanumab and the anti-Aβ approach could work in early (prodromal-to-mild) AD. Unfortunately, two subsequent phase III trials, ENGAGE (ClinicalTrials.gov, 2019q [NCT02477800]) and EMERGE (ClinicalTrials.gov, 2019m [NCT02484547]), were stopped early based on the results of the futility analyses that suggested the trials were unlikely to meet their primary endpoint. However, updated analyses of a larger dataset, that included approximately 3 months of additional data collected between the December 2018 data-cut for the futility analyses and the termination of the study in March 2019, revealed that 10 mg/kg aducanumab treatment in the EMERGE study resulted in statistically significant reduction in cognitive and functional decline (CDR-SB, MMSE, ADAS-Cog, and the Alzheimer's Disease Cooperative Study—Activities of Daily Living scale for mild cognitive impairment [ADCS-ADL-MCI]). Interestingly, the ENGAGE study did not replicate these results; however, exploratory analyses suggested that a clinical benefit could be detected in participants who received 10 or more uninterrupted 10 mg/kg doses, suggesting an exposure-dependent response. The reason for the different outcomes of the two phase III studies is unclear at this point. Nevertheless, the positive results of the PRIME phase Ib and the EMERGE phase III studies

suggest that targeting Aβ can provide clinical benefits for individuals with early AD (Biogen, 2019).

Similarly, a futility analysis stopped phase III testing (ClinicalTrials.gov, 2019p [NCT02670083]) of crenezumab, a fully humanized anti-Aβ IgG4 monoclonal antibody that targeted neutralization of Aβ oligomers, in participants with prodromal-to-mild (early) AD; the decision was based on results from a pre-planned interim analysis of the phase III CREAD study (ClinicalTrials.gov, 2019p [NCT02670083]), which indicated that the study was unlikely to meet its primary endpoint of change from baseline in CDR-SB score (F. Hoffmann-La Roche Ltd, 2019). Hence, results from *post hoc* analyses of phase II data that suggested a potential treatment effect in individuals with mild AD treated with high-dose crenezumab (Cummings, Cohen, et al., 2018) were not replicated in phase III studies, despite the fact that a fourfold higher dose was investigated. Crenezumab continues to be studied in the Alzheimer Prevention Initiative phase II primary prevention trial (ClinicalTrials.gov, 2019g [NCT01998841]) in a population at risk for autosomal-dominant AD because of a PSEN1 E280A mutation. This population is considerably younger, study participants are clinically asymptomatic at study entry, and carry a mutation that is directly implicated in Aβ metabolism.

A futility analysis also halted the phase III SCarlet RoAD study in individuals with prodromal AD when results indicated that treatment with a monthly dose of 105 mg and 225 mg of subcutaneous gantenerumab, a fully human IgG1 anti-Aβ monoclonal antibody, was unlikely to meet the primary clinical efficacy outcome (Ostrowitzki et al., 2017). Further *post hoc* exploratory analyses suggested an exposure-dependent effect on slowing cognitive decline in participants identified as "fast progressors" in whom it might have been more likely to show a treatment benefit relative to placebo within the trial period (Ostrowitzki et al., 2017). Recruitment in Marguerite RoAD, another phase III study of low-dose gantenerumab in participants with mild AD, was halted as a result of the SCarlet RoAD exploratory analyses, but dosing was continued (Abi-Saab et al., 2017; ClinicalTrials.gov, 2019d [NCT02051608]). Both Marguerite RoAD and SCarlet RoAD trials were transitioned into an open-label extension study to evaluate the safety of up to 1,200 mg of gantenerumab. Currently, the safety and efficacy of this higher dose of gantenerumab, the only anti-Aβ in late-stage development that is administered subcutaneously, is being evaluated in participants with prodromal-to-mild (early) AD in the phase III GRADUATE I (ClinicalTrials.gov, 2019n [NCT03444870]) and II (ClinicalTrials.gov, 2019f [NCT03443973]) trials. These studies are optimized to ensure a high level of cumulative drug exposure through the use of a fivefold higher dose, a titration scheme that is the same for *APOE* ε4 carriers and non-carriers. Protocols ensure minimal interruption during episodes of amyloid-related imaging abnormalities (ARIA), and treatment for the double-blind study is for a duration of 2 years (ClinicalTrials.gov, 2019n [NCT03444870]; ClinicalTrials.gov, 2019f [NCT03443973]). These studies are optimized to ensure a high level of cumulative drug exposure through the use of high-dose treatment, a titration scheme that is the same for APOE ε4 carriers and non-carriers, minimal dosing interruption during episodes of amyloid-related imaging abnormalities (ARIA), and an extended 2-year study duration (ClinicalTrials.gov, 2019n [NCT03444870]; ClinicalTrials.gov, 2019f [NCT03443973]).

Another anti-Aβ therapy that is currently under investigation is BAN2401, a humanized monoclonal antibody with high binding selectivity for soluble aggregated Aβ protofibrils (Swanson et al., 2018). Results from the phase II BAN2401 clinical trial (BAN2401-G000-201) in participants with early AD demonstrated clinical efficacy as measured by Alzheimer's Disease Composite Score (ADCOMS) (Swanson et al., 2018). Specifically, there was a significant reduction in clinical decline versus placebo at both 12 months (p = .027) and 18 months (p = .034) with the 10 mg/kg biweekly BAN2401 dose (Swanson et al., 2018). An open-label extension study to evaluate the long-term efficacy and safety of BAN2401 is also underway, allowing an extra 24 months of treatment in eligible participants from the BAN2401-G000-201 study (Swanson et al., 2019). In 2019, a phase III clinical trial evaluating the 10 mg/kg biweekly BAN2401 dose versus placebo in individuals with early AD (MCI and mild AD) was initiated (ClinicalTrials.gov, 2019k [NCT03887455]).

Lastly, treatment with donanemab (LY3002813), a humanized IgG1 anti-Aβ monoclonal antibody that recognizes the N-terminally pyroglutamate modified Aβ epitope in amyloid plaques has been evaluated in phase I studies in participants with amyloid-positive prodromal-to-moderate AD (Irizarry et al., 2016), and with MCI and mild-to-moderate AD (Fleisher et al., 2018). In the more recent phase Ib study (ClinicalTrials.gov, 2019e [NCT02624778]; Fleisher et al., 2018) donanemab significantly reduced amyloid plaque as measured by florbetapir F18 tracer uptake on PET and is currently being evaluated in a phase II trial (TRAILBLAZER-ALZ) in participants with early AD (ClinicalTrials.gov, 2019l [NCT03367403]; Irizarry et al., 2018); originally this trial included evaluation of donanemab in combination with a β-secretase inhibitor, but this arm has been discontinued.

While the efficacy varied among these agents, the main safety finding, amyloid-related imaging abnormalities indicative of vasogenic edema/effusions and hemorrhage (ARIA-E and ARIA-H, respectively), was quite similar amongst the N-terminus anti-amyloid monoclonal antibodies targeting fibrillar Aβ (e.g., bapineuzumab, aducanumab, and gantenerumab). ARIA-E incidence ranged from 3.0%–41.0%, while ARIA-H incidence ranged from 6.0%–22.9% across these molecules (Andjelkovic et al., 2018; van Dyck, 2018; Ostrowitzki et al., 2017; Salloway et al., 2014; Sevigny et al., 2016). ARIA incidence for these N-terminus anti-amyloid antibodies increased in a dose-dependent and *APOE* ε4-dependent manner (Ostrowitzki et al., 2017; Salloway et al., 2014; Sevigny et al., 2016). ARIA-E incidence ranged from 0.6%–0.9% in studies with mid-domain binding antibodies (solanezumab and crenezumab), with ARIA-H ranging from 4.9%–13.1% (Cummings, Cohen, et al., 2018; Doody et al., 2014). Phase II studies of the primarily conformational (i.e., protofibril)-binding BAN2401 antibody reported ARIA-E rates of ≤10% (ARIA-H not disclosed) (Swanson

et al., 2018). Overall, ARIA-E remains a safety concern predominantly during trials evaluating N-terminus anti-amyloid monoclonal antibody therapies.

In summary, learnings from the clinical development of anti-Aβ monoclonal antibodies helped to identify target populations that could most likely benefit from timely and sufficient exposure to anti-Aβ monotherapy. Since anti-Aβ monoclonal antibodies failed to demonstrate clinical benefit in individuals with mild-to-moderate AD, at which stage the underlying pathological changes may already escalate in an amyloid-independent fashion, targeting Aβ species in these participants may occur too late to achieve clinical benefits (Pimplikar, Nixon, Robakis, Shen, & Tsai, 2010). The lack of clinical benefit in these individuals suggests that amyloid is not the only factor involved in the pathogenesis of AD (Pimplikar et al., 2010). The pathology may include both amyloid-dependent and -independent processes (i.e., amyloid may initiate the pathophysiology in AD which eventually becomes amyloid-independent) (Hyman, 2011). Thus, anti-amyloid therapies may not carry the same clinical benefit for patients later in their disease course and, because of this hypothesis, the focus shifted to evaluating individuals at an earlier stage of disease, for example, in early (i.e., prodromal-to-mild) AD, where the neuropathological changes associated with AD may be less advanced and more dependent on the presence of amyloid (Sperling, Mormino, & Johnson, 2014). Given the continuum of AD progression and the complexity associated with AD pathology, it is highly likely that different treatments targeting various stages of the disease may be needed; a therapy demonstrating efficacy in one stage does not guarantee that the same therapy will work in another stage. Furthermore, sufficient continuous exposure to higher doses of an anti-Aβ therapy is another key learning, as demonstrated by the recent aducanumab results (Biogen, 2019). The high rate of failure associated with AD drug development has suggested that to have the best chance for treatment success, the right therapy at the right dose needs to be delivered to the right patient at the right time in the disease process, for the right duration (Cummings, Feldman, & Scheltens, 2019). However, whether this is the case because certain drugs only work at certain stages, or whether this reflects the ability of our current outcome measures and trial designs to demonstrate small treatment effects, remains to be seen.

4 | UTILIZING BIOMARKERS FOR ASSESSING TARGET ENGAGEMENT

As a result of key learnings over time, the field has evolved from one where any drug was expected to be applicable to any stage of AD, to one in which patients are targeted based upon stage of disease. The understanding of biological markers and their use in AD has therefore assumed new importance. An area of AD research in which biomarkers have demonstrated value is in the assessment of target molecule engagement. In this section, we will describe studies that evaluated target engagement of anti-amyloid therapies using imaging (e.g., PET), CSF and/or blood-based biomarkers.

In phase II testing of bapineuzumab, a reduction in PET amyloid protein load was observed (Rinne et al., 2010). Similarly, in a PET substudy of participants enrolled in the SCarlet RoAD (ClinicalTrials.gov, 2019c [NCT01224106]) and Marguerite RoAD (ClinicalTrials.gov, 2019d [NCT02051608]) open-label extension studies, gantenerumab treatment was associated with reductions in brain amyloid regardless of baseline amyloid levels or treatment subgroup. Furthermore, amyloid levels converged over 3 years regardless of treatment subgroup, with 80% of participants who completed the trial achieving levels below the positivity threshold (Klein *et al*. Data presented at CTAD 2019).

Results from the phase II BAN2401 clinical trial (BAN2401-G000-201) demonstrated a dose-dependent effect on amyloid PET in participants with early AD (Swanson et al., 2018); these reductions were statistically significant at months 12 and 18 ($p < .001$ at both time points) for participants treated with the 10 mg/kg biweekly BAN2401 dose (Swanson et al., 2018). In a recent phase Ib study (ClinicalTrials.gov, 2019e [NCT02624778]; Fleisher et al., 2018), donanemab was associated with significant and sustained reductions in amyloid plaque as measured by florbetapir F18 tracer uptake on PET. At 3 months, intravenously administered donanemab resulted in reductions in florbetapir F18 ranging from −11.8 centiloids after one dose of 10 mg/kg to −44.5 centiloids after 10 mg/kg donanemab was administered every 2 weeks (Fleisher et al., 2018).

In the phase Ib PRIME study, aducanumab treatment was associated with statistically significant dose-dependent reductions in Aβ across brain regions, except for the pons and subcortical white matter (two areas in which Aβ plaques would not be expected to accumulate) (Sevigny et al., 2016). Moreover, the updated analysis of the aducanumab phase III EMERGE and ENGAGE clinical trial interim data demonstrated that participants treated with aducanumab had a reduction from baseline in amyloid PET standardized uptake value ratio (SUVR) as well as CSF biomarkers of tau pathology (phosphorylated tau [pTau] and total tau [tTau]) versus those in the placebo group (Biogen, 2019).

The phase II BLAZE study of crenezumab demonstrated a significant increase in CSF Aβ(1–42) levels in participants treated with crenezumab as compared with placebo, suggesting target engagement in the CNS, and provided evidence of a possible slower accumulation of amyloid plaque (Salloway et al., 2018). Recent results using CSF samples from individuals who participated in phase II showed decreased CSF Aβ oligomers levels in the crenezumab group compared with placebo (Yang et al., 2018). Studies of solanezumab (phase I and II) revealed evidence of target engagement by dose-dependent increases in CSF total Aβ (Farlow et al., 2012; Siemers et al., 2010). Results from the SCarlet RoAD study suggested a dose- and time-dependent effect of gantenerumab on brain amyloid load as measured by SUVR on amyloid PET and also on a number of CSF markers that are thought to be disease-relevant, such as tTau, pTau, and neurogranin (Ostrowitzki et al., 2017).

Studies have also revealed evidence of target engagement by dose-dependent increases of total Aβ in plasma. Phase I and II studies of solanezumab demonstrated substantial dose-dependent increases in Aβ in plasma as well as in CSF (Farlow et al., 2012; Siemers et al., 2010). BAN2401, a humanized IgG1 monoclonal antibody which selectively binds and clears Aβ protofibrils (van Dyck, 2018), was investigated in a single- and multiple-ascending dose study (Logovinsky et al., 2016). Small dose-dependent increases in plasma Aβ(1–40) within a few hours after the first dose of BAN2401, and after the final dose, were reported. Plasma Aβ(1–40) levels declined over time with the fall in serum concentration of BAN2401 (Logovinsky et al., 2016). In addition, following administration of crenezumab, total plasma Aβ40 and Aβ42 have been shown to increase significantly, demonstrating target engagement in the periphery (Lin et al., 2018).

Lastly, although including imaging (e.g., PET), CSF and/or blood-based biomarkers in clinical trials can be useful for providing a better understanding of the changes in underlying AD pathology in response to treatment (Blennow, 2017), there are still considerable challenges in establishing the appropriate use of biomarkers in both AD drug development and clinical practice. It is important to note that demonstrating target engagement through biomarkers does not guarantee success in later stages of drug development (Cummings et al., 2019). Evidence of target engagement shown by a specific or the "right" biomarker, however, helps to demonstrate biological activity that may translate into clinical efficacy (Cummings et al., 2019). Biomarkers, therefore, may eventually provide surrogate outcomes in clinical trials of AD, if demonstrated to be predictive of clinical outcomes (Cummings et al., 2019).

5 | USING BIOMARKERS AS EARLY SURROGATES OF CLINICAL EFFICACY IN PHASE II TRIALS

Despite their success in demonstrating target engagement, with helping to identify patients in the very early stage of the disease, and for shaping clinical trial programs, biomarkers studied to date have not become definitive surrogates of clinical efficacy. The majority of studies to date suggest that biomarker changes alone in phase II fail to predict clinical efficacy in phase III. For example, in the phase II clinical trials evaluating the gamma-secretase inhibitor, semagacestat, there was a significant reduction in plasma Aβ(1–40) concentrations (Fleisher et al., 2008); however, no significant reduction in CSF Aβ levels and no group differences in cognitive or functional measures were observed (Fleisher et al., 2008). Phase III semagacestat findings also demonstrated no significant change on the ADAS-Cog11 and there was worsening of several clinical outcomes, including ADCS-ADL, CDR-SB, Neuropsychiatric Inventory (NPI), and MMSE (Doody et al., 2013).

Anti-Aβ immunotherapy with solanezumab revealed a dose-dependent change in plasma and CSF Aβ in phase II; however, no changes in cognitive scores occurred (Farlow et al., 2012; Siemers et al., 2010). Although the biomarker data in phase II demonstrated dose-dependent changes, in phase III testing, there was no significant change on several clinical outcomes, including ADAS-Cog11, ADCS-ADL, CDR-SB, NPI, and MMSE, following treatment with solanezumab (Doody et al., 2014). In the recently updated analysis from the EMERGE and ENGAGE trials, the subset of participants with higher exposure to aducanumab had reduced amyloid PET and performed better on the CDR-SB versus placebo (Biogen, 2019).

Amyloid biomarkers were also used to advance the BACE1 inhibitor, verubecestat (MK-8931), from phase I/II, in which results demonstrated a 90% reduction in CSF Aβ (Forman et al., 2013), to the phase II/III trial (EPOCH) in participants with mild-to-moderate AD (Egan et al., 2018); later, Merck began the phase III APECS trial in participants with prodromal AD/MCI (Egan et al., 2019). EPOCH and APECS futility analysis results both demonstrated that verubecestat did not improve cognitive and functional decline (Egan et al., 2018, 2019); participants with prodromal AD had worse cognitive decline than those treated with placebo on the CDR-SB, ADAS-Cog13, and ADCS-ADL-MCI outcome measures (Egan et al., 2019). For the BACE1 inhibitor, elenbecestat, phase II biomarker results were favorable (Lynch et al., 2018), and the drug progressed to phase III testing in the MISSION trials (ClinicalTrials.gov, 2019a [NCT02956486]; ClinicalTrials.gov, 2019b [NCT03036280]); however, these trials were terminated early because of an unfavorable risk/benefit profile (Eisai, 2019).

Findings from the phase II trials evaluating the anti-Aβ immunotherapy, bapineuzumab, demonstrated no effect on Aβ(1–42) or tTau as measured by sandwich enzyme-linked immunosorbent assay (ELISA), but results revealed a positive trend on tau181p (Salloway et al., 2009) and reduced cortical (11)C-PiB retention (Rinne et al., 2010) compared with both baseline and placebo; although neither dose/exposure response nor clear signal of potentially clinically relevant benefits was observed. The positive trends observed in phase II testing did not translate into clinical efficacy in phase III, as results demonstrated no significant changes on ADAS-Cog11 or the DAD scale in either *APOE* ε4 carriers or non-carriers following treatment with bapineuzumab (Salloway et al., 2014). Reductions in tau levels have also been observed in studies with gantenerumab. Significant reductions in CSF tTau and pTau were reported in the phase III SCarlet RoAD study, but this study did not show clinical efficacy (Ostrowitzki et al., 2017). Starting at the 105 mg dose and up-titrating to the 225 mg dose in the phase III Marguerite RoAD study was associated with a significantly greater percentage reduction in tTau and pTau versus placebo (Voyle et al., 2018). Similarly, CSF pTau levels were reduced by 13% following treatment with BAN2401 in the phase II study in early AD (Molinuevo et al., 2019). To date, reduction in CSF pTau has only been associated with improved global outcomes in the subset of participants with higher aducanumab exposure in the updated EMERGE and ENGAGE trial analyses (Biogen, 2019).

Based on the examples described earlier, the discordance between biomarkers and clinical efficacy may be because of the over-generalization of biomarkers that simply reflect the presence of

pathology to the hope that they would predict or reflect cognitive or functional benefits. First, there is no reason to assume that change in a biomarker of the underlying pathology is correlated with clinical cognitive benefits, as the established neurodegeneration would not be expected to disappear (Figure 3). Second, patient heterogeneity is an important consideration; people with the same level of neurodegeneration could have different responses to treatment based upon other factors, such as the presence of additional non-AD proteinopathies (Robinson et al., 2018) and comorbid cerebrovascular disease, being an *APOE* ε4 carrier, and possibly because of unidentified genes that either amplify neurodegeneration or provide neuroprotection (Jack et al., 2010). Thus, changes in biomarkers of underlying AD pathology may not necessarily correlate with clinical response that results from the effect of multiple underlying pathologies. It should also be considered that there are methodological differences that may account for some of the variation in results. Moreover, the findings from the updated analyses of ENGAGE and EMERGE suggest that insufficient exposure to treatment may be a factor contributing to the discordance between biomarkers and clinical efficacy. Thus, although biomarkers may not yet be definitive surrogates for clinical efficacy at this point, biomarker results have helped to shape the development of clinical trial programs and will continue to inform future clinical trial protocols.

6 | ENRICHING STUDY POPULATIONS TO DEMONSTRATE ADEQUATE PLACEBO DECLINE DURING THE LIMITED DURATION OF CLINICAL TRIALS

During AD clinical trials, participants in placebo arms worsen; however, they may decline slowly and demonstrate large and increasing variability during follow-up periods (Figure 4) (Schneider & Sano, 2009). Yet the ability to demonstrate drug–placebo differences depends upon predictable decline in the placebo group. In an analysis of nine trials with available follow-up data, the mean changes and standard deviations on different versions of the ADAS-Cog indicate that approximately 25% of participants do not worsen by more than 1 point over 18 months (Schneider & Sano, 2009). This observation may explain why modest drug effect cannot reliably be recognized during limited clinical trial periods. More importantly, it raises the question, "How can detecting efficacy be improved?". Aside from relying on stronger drug effects, strategies to address lack of placebo decline may include having a larger sample size, or recruitment strategies that focus on specific participants who are not in an advanced stage of the disease but are more likely to progress during the study period without treatment.

In active disease, the pace of progression can be predicted by the preceding rate of deterioration (Capitani, Cazzaniga, Francescani, & Spinnler, 2004). For example, the Functional Assessment Staging Test (FAST) procedure characterizes seven stages in the course of AD from normal aging to severe dementia, and progression through future FAST stages can be statistically predicted based upon progression through earlier stages (Thalhauser & Komarova, 2012). Thus, at the initial clinic visit, an assessment of the patient can predict subsequent longitudinal performance on multiple cognitive and functional measures over time (Doody et al., 2010). Using this approach, slow and intermediate progressors have been shown to diverge from the fast progressors on the ADAS-Cog over time (Figure 5) (Doody et al., 2010). This predictive relationship also holds true for global performance, ADL measures, and even mortality (Doody et al., 2010).

In addition, the clinical trial evaluating the γ-secretase inhibitor avagacestat in prodromal AD or MCI provides evidence for the potential power to select participants who are more likely to progress quickly. In the randomized prodromal AD cohort, participants had clinical symptoms of cognitive impairment but not dementia, and the CSF biomarker results were consistent with the presence

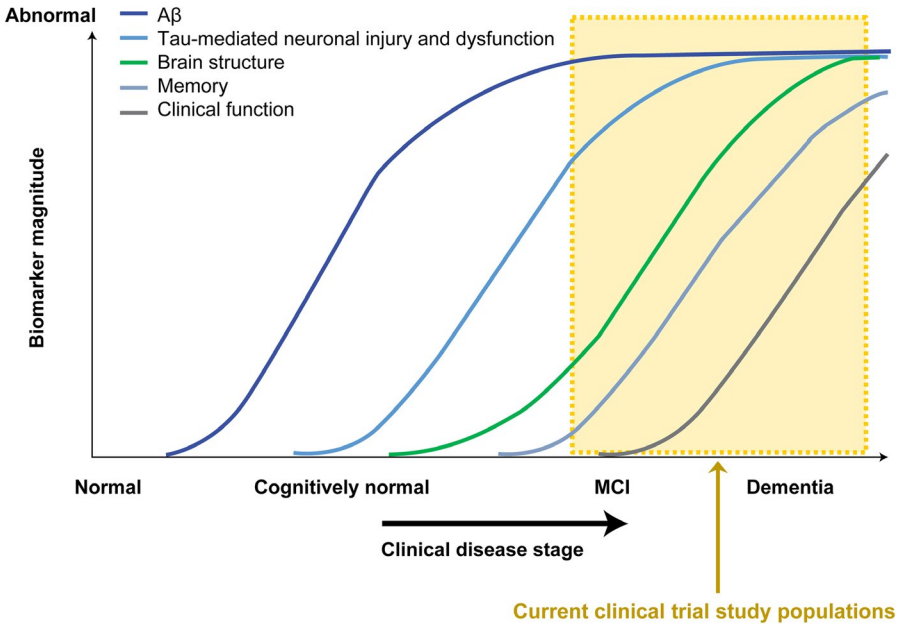

FIGURE 3 Changes in biomarker magnitude across the continuum of AD. Adapted and reprinted from Jack *et al.* *Lancet Neurol* 2010;9(1):119–128, Copyright 2010, with permission from Elsevier (Jack et al., 2010)

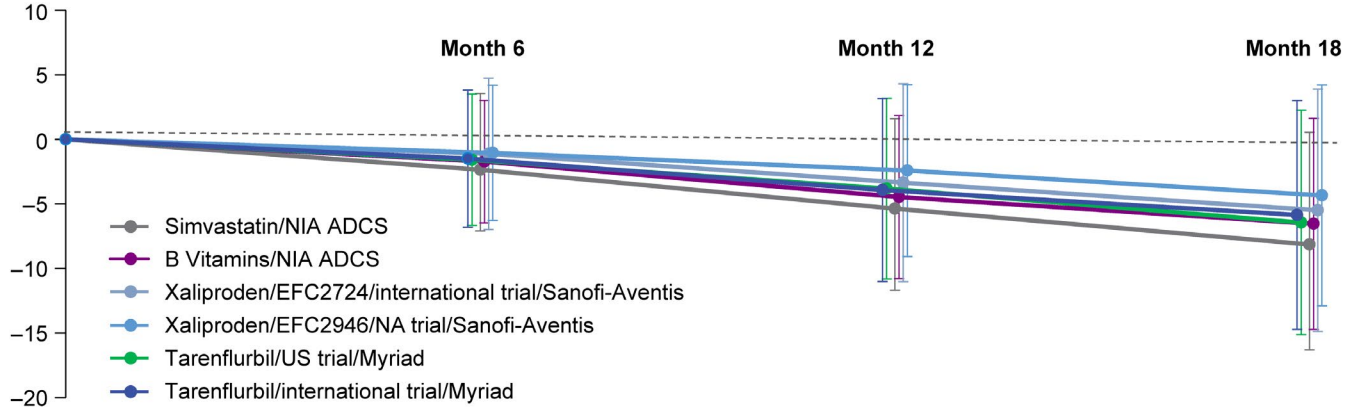

FIGURE 4 ADAS-Cog[a] mean change scores in placebo arms over 18 months of follow-up in selected clinical trials. [a]Figure includes mean (*SD*) changes from six studies using different versions of the ADAS-Cog. Reference: (Schneider & Sano, 2009)

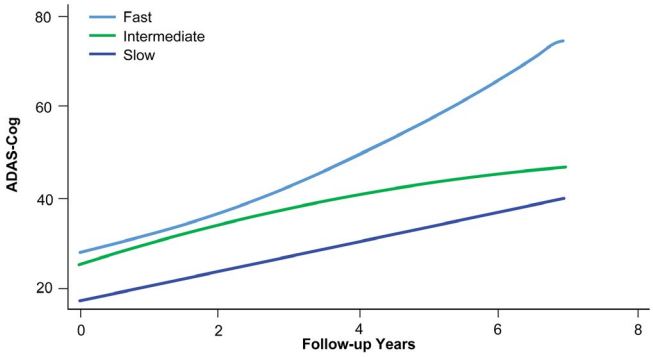

FIGURE 5 Fitted regression lines for ADAS-Cog demonstrate that slow and intermediate progressors diverge from fast progressors over time Adapted and reprinted from Doody *et al. Alzheimers Res Ther* 2010;2:2. Creative Commons Attribution 2.0 License (http://creativecommons.org/licenses/by/2.0/) (Doody et al., 2010)

of amyloidopathy (Aβ[1–42] level < 200 pg/mL or tTau:Aβ[1–42] ratio ≥ 0.39), whereas participants in the observational cohort met MCI criteria but were CSF biomarker-negative (Coric et al., 2015). Results demonstrated no significant treatment differences; but at 2 years, progression to dementia was more frequent in the prodromal AD cohort (30.7%) than in the observational cohort (6.5%) (Coric et al., 2015).

A multimodal progression model based on the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset was also able to predict progression in MCI (Delor, Charoin, Gieschke, Retout, & Jacqmin, 2013) and distinguish "slow" from "fast" progressors. Analyses of baseline covariates revealed that CDR-SB, Functional Activities Questionnaire, and hippocampal volume were the three main factors in predicting progression type; fast progressors had a baseline CDR-SB ≥ 2, Functional Activities Questionnaire ≥ 4, and hippocampal volume less than the median (i.e., Delor criteria). On the basis of these prognostic factors, 81% of MCI participants could correctly be assigned to the slow- or fast-progressing subpopulations and 77% of MCI-to-AD conversions could be predicted (Delor et al., 2013).

In an exploratory *post hoc* analysis of the SCarlet RoAD trial, gantenerumab showed exposure-dependent effects in the slowing of cognitive decline in fast progressors identified by the above-mentioned Delor criteria (Delor et al., 2013; Lasser et al., 2015; Ostrowitzki et al., 2017), indicating that increased drug exposure can lead to detectable treatment effects. Fast progressor participants were classified into placebo, low-, medium-, and high-exposure groups based on estimated average serum concentrations computed by population pharmacokinetic analysis. Participants with low concentrations showed a median 1-point improvement in cognition compared with placebo; participants with medium concentrations showed a median 2-point improvement compared with placebo; and participants with high concentrations showed a median 3-point (50%) improvement compared with placebo. Similar trends were observed for MMSE and Cambridge Neuropsychological Test Automated Battery (CANTAB); however, it should be noted there was no trend observed for CDR-SB (Ostrowitzki et al., 2017; Retout et al., 2015).

In the crenezumab trials, inclusion criteria in the phase II ABBY and BLAZE studies required participants to have a CDR-SB score ≥ 0.5 and MMSE of 18–26 points (Cummings, Cohen, et al., 2018; Salloway et al., 2018). Biomarkers were evaluated in the BLAZE study (Salloway et al., 2018) and biomarker inclusion criteria were also incorporated into the phase III CREAD study protocol (Sink, Ostrowitzki, et al., 2019; Sink, Warren, et al., 2019). Moreover, CREAD participants were required to have a CDR Global Score of 0.5 or 1 and MMSE ≥ 22, as well as a Free and Cued Selective Reminding Test (FCSRT) free recall of ≤ 27 and cueing index ≤ 0.67 (Sink, Ostrowitzki, et al., 2019; Sink, Warren, et al., 2019), in addition to amyloid pathology criteria: PET scan positive for cerebral amyloid-β and CSF Aβ(1–42) per the Elecsys® β-Amyloid(1–42) CSF immunoassay (ClinicalTrials.gov, 2019p [NCT02670083]; ClinicalTrials.gov, 2019o [NCT03114657]). Incorporating FCSRT as part of the CREAD inclusion criteria was based on analyses of the phase III SCarlet RoAD trial (ClinicalTrials.gov, 2019c [NCT01224106]), which indicated that a cueing index cut-off value of 0.67 in that study helped to distinguish individuals who progressed on CDR-SB within a 24-month period from those who did not (Smith et al., 2016). Performance on the

FCSRT helps to identify participants with an elevated risk of developing AD dementia (Grober, Veroff, & Lipton, 2018), thus increasing the potential of enriching a clinical trial population with individuals with early AD who are likely to progress during the study. Since the ability of a DMT to demonstrate efficacy versus placebo is based partly on the rate of decline, or progression, observed within the placebo group, the trajectory of the placebo group helps to determine the treatment difference at the end of a clinical trial (Cummings, Ritter, & Zhong, 2018). Although the CREAD trials were stopped early for low likelihood of meeting the primary endpoint, inadequate progression in CDR-SB was not a contributing factor in either the prodromal or mild AD subgroups (Sink et al. Data presented at CTAD 2019). In addition, almost half of participants screened for CREAD failed early in the screening process because of not meeting the FCSRT inclusion criteria; thus, the cueing index may have helped to identify a population likely to decline and with higher rates of progression (Sink et al. Data presented at CTAD 2019). Incorporating inclusion criteria such as FCSRT helps to identify a trial population likely to decline and with higher rates of progression, which may improve the power of clinical trials to detect efficacy and may allow for more efficient trials in early AD. However, a potential caveat associated with enriching for progressors may be that these individuals are potentially also less likely to respond to therapy, especially with anti-Aβ monotherapy.

An additional strategy to improve efficacy findings by way of enriching study populations may be to exclude older patients from clinical studies. Age-related decrements across multiple cognitive domains, including memory, working memory/executive functions, regardless of AD status, are well established (Mormino & Papp, 2018). Furthermore, elderly patients with AD typically present with multiple comorbid neuropathological abnormalities unrelated to amyloid that further contribute to cognitive loss (Kawas et al., 2015; White et al., 2016). In addition, with increased age, the likelihood of multiple co-pathologies being present also increases, which may in turn contribute to the severity of dementia (Kawas et al., 2015). Together, the age-related cognitive decline and increased likelihood of comorbidities in older AD patients may mask any treatment-related efficacy signals, particularly within the short duration of traditional phase III studies.

7 | SUMMARY

In summary, targeting the potentially modifiable risk factors for AD does not appear to benefit individuals with manifest AD; however, targeting multiple AD risk factors with a multidomain intervention (e.g., a combination of diet, exercise, and lifestyle change) in asymptomatic, at-risk populations, may provide cognitive benefit to people at risk for AD and could delay the onset of dementia. Confirmation of this hypothesis with respect to dementia has yet to be evaluated. Based on the continuum of AD progression, it is unlikely that the same drug or DMT will benefit all stages of disease; thus, selecting the "right" trial participant to use the "right" DMT at the "right" time along the continuum, and for the "right" duration, may be of importance in trials evaluating therapies for AD. Furthermore, biomarkers have demonstrated great value in assessing target engagement in different clinical trial populations and have helped to make it possible to identify individuals who are on the pathway to development of AD in the prodromal stage. Although the relationship between biomarkers and clinical efficacy is still under investigation, the updated analyses from the phase III EMERGE and ENGAGE aducanumab studies have generated evidence to examine the link between biomarker changes and clinical efficacy, although these data have not yet been presented or published. Lastly, applying clinical participant selection criteria to bolster signal detection in clinical trials can be predictably accomplished. Most of these advances have become apparent through learnings in AD clinical trials that did not meet their clinical efficacy goals, but nonetheless advanced the field.

8 | CONCLUSIONS

In conclusion, a lot has been learned over the years about what does and does not work in selecting treatments for evaluation, selecting participants for clinical trials, and measuring efficacy; but we are still not where we need to be in preventing and treating AD. While targeting amyloid accumulation in symptomatic stages of AD may not provide the full level of disease modification that is ultimately needed, it is likely to make a lasting difference in the progression of disease. The field will advance, not all at once, but through successful trials of stage-dependent treatments, probably delivering with small effect sizes as a beginning, which will then stimulate the level of investment needed to develop even more definitive approaches. The treatment of AD will likely require combinations of therapies and brain protection strategies at every stage along the continuum of the disease.

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