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Review

Antibody-Mediated Clearance of Brain Amyloid-β: Mechanisms of Action, Effects of Natural and Monoclonal Anti-Aβ Antibodies, and Downstream Effects

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Abstract. Immunotherapeutic efforts to slow the clinical progression of Alzheimer's disease (AD) by lowering brain amyloid-β (Aβ) have included Aβ vaccination, intravenous immunoglobulin (IVIG) products, and anti-Aβ monoclonal antibodies. Neither Aβ vaccination nor IVIG slowed disease progression. Despite conflicting phase III results, the monoclonal antibody Aducanumab received Food and Drug Administration (FDA) approval for treatment of AD in June 2021. The only treatments unequivocally demonstrated to slow AD progression to date are the monoclonal antibodies Lecanemab and Donanemab. Lecanemab received FDA approval in January 2023 based on phase II results showing lowering of PET-detectable Aβ; phase III results released at that time indicated slowing of disease progression. Topline results released in May 2023 for Donanemab's phase III trial revealed that primary and secondary end points had been met. Antibody binding to Aβ facilitates its clearance from the brain via multiple mechanisms including promoting its microglial phagocytosis, activating complement, dissolving fibrillar Aβ, and binding of antibody-Aβ complexes to blood-brain barrier receptors. Antibody binding to Aβ in peripheral blood may also promote cerebral efflux of Aβ by a peripheral sink mechanism. According to the amyloid hypothesis, for Aβ targeting to slow AD progression, it must decrease downstream neuropathological processes including tau aggregation and phosphorylation and (possibly) inflammation and oxidative stress. This review discusses antibody-mediated mechanisms of Aβ clearance, findings in AD trials involving Aβ vaccination, IVIG, and anti-Aβ monoclonal antibodies, downstream effects reported in those trials, and approaches which might improve the Aβ-clearing ability of monoclonal antibodies.

Keywords: Alzheimer's disease, amyloid-β, amyloid hypothesis, antibodies, clearance, clinical trials, downstream effects, intravenous immunoglobulin

The number of Americans 65 years of age and older with Alzheimer's disease (AD) was estimated by the Alzheimer's Association in its "2022 Alzheimer's Disease Facts and Figures" report to be 6.5 million and is expected to increase to nearly 13 million by 2050 [1]. That report indicated that caregivers for people with dementia are twice as likely to report emotional, financial, and physical problems as caregivers of non-demented individuals. These statistics underscore the importance of developing treatments to slow the clinical progression of AD in order to improve the quality of life for AD patients and their caregivers.

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AD's hallmark neuropathological findings are amyloid-β (Aβ)-containing plaques and tau protein-containing neurofibrillary tangles. The plaques may be neuritic plaques (also referred to as senile plaques [SP]), which contain dense cores of fibrillar Aβ as well as dystrophic, tau paired helical filament-containing neurites [2], or they may be diffuse plaques, containing filamentous Aβ and lacking dense cores. Although diffuse plaques generally do not contain neurites, they may do so in late-stage AD [3]. The amyloid hypothesis, published by Hardy and colleagues in the early 1990 s [4, 5], postulated that increased deposition of fibrillar Aβ initiated AD-type pathology. The hypothesis was challenged by findings of increased SP densities in some subjects with little or no cognitive impairment [6], weak correlations between SP densities, insoluble Aβ levels, and PET-detectable Aβ with measures of cognitive impairment [7–10], and failures of Aβ-targeting approaches in large-scale AD clinical trials [11–13]. The hypothesis was subsequently revised to suggest that Aβ oligomers may initiate AD pathology [14, 15]. Since publication of the hypothesis, efforts to slow AD's progression have focused primarily on lowering of brain Aβ. Aβ can be cleared from the brain by enzymatic degradation and by efflux from the brain. It is degraded via the endosomal-lysosomal system [16], the ubiquitin-proteasome system [17], and autophagy [18]; Aβ efflux from the brain is via the blood-brain barrier (BBB) [19], the blood cerebrospinal fluid (CSF) barrier [20], glymphatic (paravascular) drainage [21], and perivascular drainage [22]. Antibody binding to Aβ promotes clearance of cerebral Aβ by several mechanisms, as discussed below.

Approaches which have attempted to slow AD's progression by lowering brain Aβ have included Aβ vaccination [23], Aβ aggregation inhibitors [24], β-secretase inhibitors [25], γ-secretase modulators [26], γ-secretase inhibitors [27], intravenous immunoglobulin (IVIG) products [28, 29], and monoclonal anti-Aβ antibodies [30–32]. Most of these approaches have failed to meet primary end points in large-scale clinical trials, with the notable recent exceptions of some monoclonal antibodies. Statistically significant treatment effects for some measures of cognition were reported in 2014 in a phase III trial for a monoclonal antibody, Solanezumab, but the antibody did not meet its primary end point in either of its phase III trials [31]. Conflicting results in two phase III trials were reported in 2019 for the monoclonal antibody Aducanumab [33, 34]. Despite a recommendation from the Unites States Food and Drug Administration (FDA) advisory board not to approve it, Aducanumab received FDA approval for treatment of AD in June 2021 based on its ability to reduce PET-detectable Aβ. Another monoclonal antibody, Lecanemab, was approved for treatment of AD by the FDA in January 2023 based on results in its phase IIb trial [35]. Although Lecanemab failed to meet its primary end point in that trial, bi-weekly administration of the highest dose of the antibody produced a significant reduction in PET-detectable Aβ. In a later phase III trial, Lecanemab did meet its primary end point [36]. The monoclonal antibody Donanemab was shown, in topline results announced in May 2023, to have met its primary end point and all secondary end points in a phase III trial [37]. Donanemab's manufacturer Lilly has indicated that it intends to pursue regulatory approval for the antibody in the near future.

Grifols Biologicals' AMBAR (Alzheimer Management by Albumin Replacement) clinical trial [38, 39], in which AD patients underwent plasmapheresis with albumin replacement, intended to reduce cerebral Aβ levels by a "peripheral sink" mechanism (discussed below). AMBAR was a phase IIb trial in the United States and a phase III trial in Europe. Results were published by Boada et al. [38]. Slowing of disease progression in comparison with sham-treated subjects was achieved based on some measures of cognition (Alzheimer's Disease Assessment Scale–Cognitive subscale [ADAS-Cog] and Alzheimer's Disease Cooperative Study-Activities of Daily Living [ADCS-ADL]; *p*-values were 0.05 and 0.002, respectively, for patients with moderate AD (Mini-Mental State Examination [MMSE] scores of 18-21), while the differences in ADAS-Cog and ADCS-ADL scores between treated and sham-treated subjects with mild AD (MMSE scores 22-26) were not statistically significant, possibly due in part to an unexpected slowing of disease progression in the sham-treated mild AD patients. Whether the slowing of disease progression in patients with moderate AD was due to lowering of brain Aβ was unclear. The inclusion criteria for AMBAR included clinical diagnosis of AD and MMSE scores between 18 and 26 [40], but eligible subjects were not screened for PET-detectable Aβ so the possibility that some of the study subjects may not have had AD cannot be ruled out.

Prior to the recent successes with some monoclonal anti-Aβ antibodies, several reasons were suggested for the failure of this and other approaches to significantly slow AD clinical progression in large-scale

trials. The reasons included inappropriate selection of study subjects in some trials (i.e., inclusion of individuals with the clinical diagnosis of AD but without biomarker evidence of increased cerebral Aβ, or individuals with too advanced disease) [12], targeting of the wrong pathological substrates [12, 41], antibody-resistant Aβ conformations [42], initiation of treatment too late in the disease process, inappropriate drug dosages, and the possibility that combination treatments rather than monotherapy may be required [41]. The possibility was also suggested that Aβ may not be an appropriate therapeutic target (or not the best target) for slowing AD progression [11, 43–46].

The ability of anti-Aβ monoclonal antibodies to slow AD progression may depend not only on the extent to which the antibodies lower soluble and/or insoluble Aβ levels in the brain, but also on their effects on neuropathological mechanisms suggested by the amyloid hypothesis to occur downstream of Aβ aggregation. This review discusses the mechanisms by which antibodies are known to promote clearance of brain Aβ, the effects of Aβ binding by vaccine-induced antibodies, naturally-occurring antibodies ("natural antibodies"), and monoclonal antibodies, the downstream effects reported for treatment with these antibodies in clinical trials, and approaches which might increase the ability of anti-Aβ monoclonal antibodies to reduce cerebral Aβ.

MECHANISMS OF ANTIBODY-MEDIATED CLEARANCE OF CEREBRAL Aβ

Microglia are the resident macrophages of the brain's immune system [47, 48]. When antibodies bind via their Fab ("fragment antigen-binding) regions to fibrillar Aβ, the Fc ("fragment crystallizable") portions of the antibodies are available for binding to microglia by microglial Fc receptors (FcR). Binding of the Fc portion of an antibody to microglial FcR activates the microglia and increases their phagocytic ability [49, 50]. However, treatment with anti-Aβ antibodies may also induce a shift in microglial activation phenotype from anti-inflammatory (M2) to pro-inflammatory (M1), decreasing the ability of the microglia to clear Aβ [51]. The microglial M1 phenotype is characterized by production of pro-inflammatory molecules including cytokines such as tumor necrosis factor-α, interleukin (IL)-1, and IL-6, as well as chemokines, prostaglandins, and reactive oxygen species [47], whereas M2-activated microglia produce anti-inflammatory cytokines including IL-4, IL-10, IL-13, and transforming growth factor-β [52, 53]. (A switch in microglial activation phenotype from M2 to M1 has also been suggested to occur during AD progression [54–57]). Microglial uptake of Aβ is facilitated by other "pattern recognition receptors" in addition to FcRs (reviewed by Ries and Sastre [58]) including low density lipoprotein receptor related protein 1 (LRP1) [59], complement receptors [60, 61], formyl peptide receptors [62], scavenger receptors [63], and toll-like receptors [64]. Whether microglial uptake of soluble Aβ is via phagocytosis or fluid-phase macropinocytosis is unclear [65]. Interestingly, microglial uptake of fibrillar Aβ may decrease in the presence of oligomeric Aβ [66].

In addition to microglia, other cells in the CNS also express FcRs (reviewed by Okun et al. [67]) including neurons [68], astrocytes [69, 70], oligodendrocytes [71], and dendritic cells [72], but it is unclear if these cells can phagocytose antibody-bound Aβ. Uptake of complexes containing antibody bound to the extracellular Aβ domain of amyloid-β protein precursor (AβPP) was reported for neuroblastoma cells and primary neurons; after internalization, APP was transported to early endosomes, then cleaved by beta-site amyloid precursor protein cleaving enzyme (BACE) [73]. Antibody-mediated uptake of Aβ by neurons was reported in another study [74] but the source of the antibodies in that study was sera from AD patients, and the antibodies which bound to Aβ were hypothesized to be "brain-reactive" rather than Aβ-specific. The possibility that neurons may phagocytose antibody-Aβ complexes is supported by reports of neuronal endocytosis of antibodies bound to other antigens such as tau [75, 76] and gangliosides [77]. Astrocytes phagocytose Aβ [78–80] but no reports were found of antibody-mediated promoting of this process for these cells; in fact, one study found the opposite result: incubating Aβ with anti-Aβ antibodies prevented its degradation by astrocytes [81]. Phagocytosis by astrocytes is an emerging area of investigation which was recently reviewed by Konishi et al. [82]. That review discussed crosstalk between astrocytes and microglia. Astrocytes can promote microglial phagocytosis, whereas pro-inflammatory microglia or microglia activated by triggering receptor expressed on myeloid cells 2 (TREM2) may inhibit astrocytic phagocytosis. Oligodendrocytes have also been reported to phago-

cytose Aβ [83], although Aβ may be cytotoxic to these cells [84].

In addition to phagocytosis, antibody binding to Aβ can promote microglial uptake of Aβ indirectly, by activating the classical complement pathway [85, 86]. Three complement activation mechanisms are known, namely the classical, alternative, and lectin-binding pathways. Crosslinking of C1q, the first protein in the classical complement pathway, between adjacent Fc portions of immunoglobulin G (IgG) molecules bound to a cell surface antigen activates the classical complement cascade. This pathway can also be activated by C1q binding to the Fc portion of a single immunoglobulin M (IgM) molecule [87]. The classical and alternative complement pathways can also be activated by fibrillar Aβ, promoting its uptake by microglia [85, 88, 89]. When anti-Aβ antibody levels are suboptimal for promoting microglial phagocytosis of antibody-Aβ complexes, microglial uptake of these complexes can be facilitated by binding of C1q to the antibodies [60]. Complement activation has been characterized as a "double-edged sword" because early complement activation proteins promote clearance of Aβ, whereas complete complement activation generates the neurotoxic membrane attack complex C5b-9 [90, 91].

Anti-Aβ antibodies have been shown to reduce brain Aβ by other mechanisms in addition to promoting microglial phagocytosis (reviewed by Deane et al. [19] and Morgan [92]). Surprisingly, studies in transgenic mouse models of AD found that uptake of anti-Aβ antibodies via microglial FcR did not account for the majority of antibody-mediated clearance of SPs [93] and microglia were not required for immunotherapeutic clearance of SP to occur [94, 95]. Non-microglial mechanisms of antibody-mediated Aβ clearance include dissolving of Aβ aggregates [94, 96, 97] (anti-Aβ antibodies were also reported to inhibit Aβ aggregation [98]) and promoting efflux of antibody-Aβ aggregates from the brain via the BBB, after binding of these complexes to BBB receptors including LRP1 and the neonatal FcR [99, 100]. The expression of LRP1 on brain endothelial cells has been suggested to decrease during normal aging [101, 102] and in AD [103, 104], which could reduce the ability of antibodies to clear Aβ from the brain via this mechanism. However, other studies found increased LRP1 expression in AD [105, 106].

A final mechanism by which antibodies may promote clearance of cerebral Aβ is via "peripheral sink" activity [107, 108], mentioned above in conjunction with the AMBAR trial. The peripheral sink hypothesis postulates that peripheral blood anti-Aβ antibodies do not need to enter the brain to promote clearance of brain Aβ (and if the antibodies do enter the brain, this may reduce their peripheral sink activity [19]). Rather, antibody binding to Aβ in peripheral blood may change the equilibrium between circulating and brain Aβ levels, resulting in increased efflux of soluble Aβ from the brain via LRP1 expressed on the BBB [101, 109]. Binding of antibodies to Aβ in peripheral blood may also lower brain Aβ levels by reducing the influx of Aβ into the brain via its binding to the receptor for advanced glycation end products [19]. Peripheral sink-mediated efflux of Aβ from the brain may also be induced in the absence of anti-Aβ antibodies, by binding of Aβ to peripheral blood proteins such as albumin [110, 111] and soluble LRP1 (sLRP1), which is generated by proteolytic cleavage of cell-surface LRP1 [112]. It should be noted that some investigators have challenged the validity of the peripheral sink hypothesis [113, 114].

NATURALLY OCCURRING ANTI-Aβ ANTIBODIES (NABS-Aβ)

Antibodies which bind to Aβ are found in peripheral blood and CSF in non-cognitively impaired subjects as well as individuals with AD. These antibodies have been referred to as natural antibodies to Aβ (Nabs-Aβ) [115–117]. Natural antibodies typically have broad reactivity ("polyreactivity") against self antigens [118, 119] and low antigen-binding affinity and may be generated in the absence of antigenic stimulation (i.e., they may not be truly antigen-specific) [120]. Conflicting findings have been published as to whether the levels of peripheral blood antibodies to Aβ differ between AD patients and non-cognitively impaired subjects; the levels of these antibodies in AD have been reported to be decreased [121–128] or increased [129, 130]. A recent study found that plasma antibodies to Aβ's N-terminus increased during AD progression while antibodies to its mid-domain decreased [117]. Because of IgG's large size (molecular weight ca. 150 kDa), under normal conditions peripheral blood IgG is almost completely excluded from the brain; in normal mice, only 0.1% of systemically-administered IgG crosses the BBB [131, 132]. However, in AD, BBB damage is an early event [133–135] and likely increasing the penetration of peripheral blood IgG into the brain [136–138]. Whether the levels of peripheral blood anti-Aβ antibodies entering the

brain are sufficient to promote Aβ clearance is unknown. This was suggested by a study which detected IgG binding to SPs in AD brain specimens (although the antigenic specificity of the IgG was not determined), with decreased SP numbers in specimens in which IgG immunoreactivity on SPs was prominent [139]. Other investigators have also reported the presence of IgG (or its light chains) of unknown antigenic specificity on SPs [140–143]. The possibility that peripheral blood antibodies to Aβ may enter the brain and slow AD's neuropathological progression was also suggested by the finding of an inverse association between the level of CSF anti-Aβ antibodies and atrophy of medial temporal structures including hippocampus, entorhinal cortex, and amygdala in patients with AD but not in patients with amnestic mild cognitive impairment (MCI) or non-AD dementia [144]. Whether anti-Aβ antibody levels in CSF differ between AD and non-demented subjects has not been extensively investigated, although one study found lower levels of these antibodies in AD CSF [121]. Anti-Aβ antibodies have also been reported in CSF from patients with cerebral amyloid angiopathy (CAA), which is often present in AD [145, 146]. BBB damage occurs in CAA [147, 148] and may increase passage of peripheral blood anti-Aβ antibodies into the brain.

IVIG products, which are prepared from plasma immunoglobulins from large numbers (usually > 10,000) of healthy donors, contain Nabs-Aβ [149–151]. Aβ-related effects which have been reported for IVIG or its purified anti-Aβ antibodies include dissolving of Aβ fibrils and promoting of Aβ phagocytosis [152], inhibiting of Aβ oligomer formation [151], and protecting of SH-SY5Y neuroblastoma cells from the cytotoxic effects of Aβ oligomers [153]. In addition to Nabs-Aβ, IVIG products also contain specific antibodies to non-phosphorylated tau (recombinant human tau peptide, Tau-441, 2N4 R) and phosphorylated tau (p-tau-199 and p-tau-202) [154, 155], and they exert anti-inflammatory and antioxidant effects [156–160]. Administration of IVIG to transgenic mouse models of AD produced conflicting results for its ability to prevent Aβ pathology and clear Aβ from the brain [153, 161, 162]. A recent study found that treatment of TgCRND8 mice with IVIG reduced hippocampal plaques, an effect that was increased by the use of focused ultrasound to increase cerebral uptake of the IVIG [163]. Based on the presence of anti-Aβ antibodies in IVIG, and the possibility that peripheral blood anti-Aβ antibodies may be reduced in AD patients (therefore, administering these antibodies might have beneficial effects in AD) [161], the effects on AD progression of two IVIG products, Octapharma's Octagam and Baxter Healthcare's Gammagard, were investigated in phase II and phase III trials respectively. Neither product slowed cognitive decline in AD patients compared to placebo-treated AD patients [28, 29].

INITIAL ATTEMPT WITH Aβ IMMUNOTHERAPY: THE AN1792 VACCINATION TRIAL

The development of transgenic mice expressing the human APP, presenilin 1, and presenilin 2 gene mutations associated with early onset AD [164–169] led to studies of the effects of active immunization (Aβ vaccination) and passive immunization (systemic administration of monoclonal anti-Aβ antibodies) in these mice. Vaccination of young PDAPP mice with $A\beta_{1\text{-}42}$ prevented development of SPs, neuritic dystrophy, and astrocytosis, while vaccination of older PDAPP mice decreased this pathology [170, 171]. These results were confirmed by other investigators [95, 172–174] leading to the AN1792 clinical trial in which AD patients ($n = 300$) were vaccinated with Aβ plus the adjuvant QS-21 in the emulsifying agent polysorbate 80; a control group of AD patients ($n = 72$) were administered saline. The trial was stopped after meningoencephalitis developed in 18 (6%) of the vaccinated subjects [23, 175–178]. Meningoencephalitis was later suggested to have been caused by induction of a proinflammatory T lymphocyte response by the QS-21 adjuvant [179, 180] and/or the presence of the dominant T cell epitope $A\beta_{10\text{-}24}$ in the vaccine preparation [181]. An antibody response to the vaccine, prospectively defined by the study investigators as a serum anti-Aβ IgG titer $\geq 1:2{,}200$, was achieved in only 20% of the vaccinated subjects [23]. The inability of many of the subjects to qualify as "antibody responders" was suggested to have been due to immunological tolerance or an age-associated decline in their immune responsiveness [182]. The antibodies induced by the vaccine were primarily against Aβ's N-terminal amino acids [183, 184], a finding replicated in PSAPP mice [174]. Although postmortem examinations on some of the vaccinated subjects revealed marked reductions in SP numbers [177, 184–186], no significant differences were found between "antibody responder" subjects and placebo-treated subjects for measures of clinical

disease progression [23], and when all study subjects were considered, immunization did not improve survival time or time to severe dementia [187]. The development of meningoencephalitis in some of the subjects led to studies in transgenic mouse AD models of the effects of immunization with different Aβ peptides [174, 188–193], as well as the effects in these AD models of monoclonal antibodies targeting different Aβ epitopes [12, 194–199]. Both approaches reduced SP numbers and slowed development and progression of cognitive and memory deficits in the mouse models. These findings led to clinical trials investigating the effects of humanized or fully human monoclonal anti-Aβ antibodies, and also IVIG, in AD patients.

MONOCLONAL ANTI-Aβ ANTIBODIES IN CLINICAL TRIALS

Monoclonal anti-Aβ antibodies whose efficacy in AD patients has been evaluated in phase II or phase III clinical trials are shown in Table 1.

The monoclonal antibodies bind to different regions of Aβ, including its N-terminal amino acids (which influence Aβ's ability to aggregate [202] and are accessible for antibody binding to fibrillar Aβ [203–205]), its central domain, its C-terminal residues (whose binding by antibodies in peripheral blood should result in sequestering of Aβ in peripheral blood [206, 207]), and conformation-specific epitopes such as pyroglutamate-bound Aβ, which is present on SPs [208]). (The monoclonal antibody Donanemab binds to an N-terminal epitope on $Aβ_{p3\text{-}42}$, a species of Aβ in which the first two N-terminal amino acids have been removed by proteases and a pyrol ring has been formed at the N-terminus; the latter modification is termed pyroglutamate. $Aβ_{p3\text{-}42}$ is likely SP-specific [209]). Although anti-Aβ antibodies bind to linear epitopes, they are also able to recognize conformational epitopes [210, 211], and this may account for the specificities of the monoclonal antibodies to different Aβ conformations. Aducanumab was developed from blood lymphocytes collected from elderly subjects without cognitive impairment or with unusually slow cognitive decline [212, 213], so it may be considered to be a naturally-occurring antibody. In contrast to the neuroprotective effects of systemically administered anti-Aβ monoclonal antibodies in mouse AD models [212, 214–217], some studies have suggested that antibody binding to some Aβ epitopes (particularly its N-terminal amino acids) may result in (or may be associated with) a shift in AβPP proteol-

Table 1
Anti-Aβ monoclonal antibodies whose efficacy in AD patients has been evaluated in phase II and/or phase III clinical trials. The antibodies target different Aβ epitopes and bound different conformations of Aβ

Antibody	IgG Subclass	Aβ Sequence Targeted	Aβ Conformation Specificity	Highest Trial Phase Completed
Bapineuzumab	IgG1 (humanized mouse mAb 3D6)	$Aβ_{1\text{-}5}$	Monomers, oligomers, fibrils	III
Solanezumab	IgG1 (humanized mouse mAb m266)	$Aβ_{16\text{-}26}$	Monomers	III
Ponezumab	IgG2 (humanized; similar to mouse mAB 2H6)	$Aβ_{33\text{-}40}$	Monomers	II
Crenezumab	IgG4 (humanized)	$Aβ_{13\text{-}24}$	Monomers, oligomers, fibrils	III
Gantenerumab	Human IgG1	$Aβ_{2–11}$ and $Aβ_{18–27}$	Oligomers, fibrils	III[a]
Aducanumab	Human IgG1	$Aβ_{3\text{-}7}$	Oligomers, fibrils	III[b]
Lecanemab	IgG1 (humanized mouse mAb158)	$Aβ_{1\text{-}16}$	Oligomers, protofibrils[d], fibrils	III[c]
Donanemab	humanized IgG1 (developed from mouse IgG2a mE8)	$Aβ_{p3\text{-}42}$	Fibrils	III[e]

[a]Gantenerumab phase III and phase III trials were terminated based on futility analysis; both were continued as open-label extensions. A phase III secondary prevention trial, SKYLINE, is in progress. [b]Aducanumab's phase IIIb open-label study EMBARK, for previous Aducanumab trial participants, is in progress; phase IV confirmatory trial ENVISION is planned. [e]Lecanemab's phase III trial AHEAD 3-45 is in progress. [d]Lecanemab's binding to Aβ oligomers and protofibrils is approximately 10–15 fold greater than its binding to Aβ fibrils [35]. [e]Donanemab's phase III trial TRAILBLAZER-ALZ 2 has been completed. Phase III trials TRAILBLAZER-ALZ 3, TRAILBLAZER-ALZ 4, and TRAILBLAZER-ALZ 5 are in progress. Table includes information (used with permission) from Dong et al., *Int J Mol Sci*, Multidisciplinary Digital Publishing Institute [200] and Tian Hui Kwan et al., *Dement Geriatr Cogn Disord*, S Karger AG, Basel [201].

ysis from α-secretase to β-secretase cleavage [218], increased Aβ production [117, 219], and increased Aβ-mediated neurotoxicity [205]. Whether any of these effects occurred in the monoclonal antibody clinical trials is unknown.

The abilities of the monoclonal anti-Aβ antibodies investigated in large-scale AD trials to reduce insoluble (PET-detectable) brain Aβ levels have varied. It should be noted that although "PET-detectable Aβ" is primarily associated with neuritic plaques, the radioligands used for PET detection of Aβ can also bind to diffuse plaques and to Aβ deposited as CAA [220], and PET cannot differentiate between parenchymal and vascular amyloid [221]. Ikonomovic et al. [220], discussing PET detection of Aβ, stated that "Although it has become commonly assumed that diffuse plaques do not contain fibrillar amyloid, electron microscopic observations have indicated that diffuse plaques contain sparse, loosely-textured amyloid fibrils ... fibrillar amyloid is often present, although at lower densities than within neuritic or core-only plaques". Thus, while data indicating the extent to which anti-Aβ monoclonal antibodies have reduced PET-detectable Aβ in clinical trials likely reflect mainly the effects of these antibodies on neuritic plaques, the data are not specific for neuritic plaques because some clearance of diffuse plaques and/or of CAA-associated Aβ may also have occurred. Reductions in PET-detectable Aβ for the monoclonal antibodies which targeted Aβ's N-terminal amino acids (summarized by Liu et al. [117]) were: Bapineuzumab, 20%; Gantenerumab, nearly 100%; Donanemab, 70%; Aducanumab, 70%; and Lecanemab, 70%. (Note, however, that in Lecanemab's phase IIb study, the highest dose of the antibody, administered bi-weekly, lowered PET-detectable Aβ by up to 93% [35, 222]), and in Donanemab's TRAILBLAZER-ALZ3 phase III trial [37], treatment was stopped when PET-detectable Aβ decreased to levels considered to be "negative for pathology" according to criteria defined by a previous study [223]). Although some of the monoclonal antibodies bind to soluble Aβ conformations (monomers, oligomers, and protofibrils), the extent to which brain levels of these Aβ conformations may have been reduced in the clinical trials is unknown because soluble Aβ is not detectable with currently available PET radioligands [224]. Interestingly, Crenezumab, which targets $A\beta_{13\text{-}24}$, binds to both monomeric and aggregated forms of Aβ, with highest affinity to Aβ oligomers [225], but no significant difference between Crenezumab-treated and placebo-treated subjects was found in pooled data from two phase III trials for the change from baseline in CSF Aβ oligomer concentration. This finding suggested that clearance of cerebral Aβ oligomers by the antibody may have been poor.

COMPARISON OF THE EFFECTS OF SOLANEZUMAB, ADUCANUMAB, LECANEMAB, AND DONANEMAB ON CLINICAL PROGRESSION OF AD, PET-DETECTABLE Aβ, AND AMYLOID-RELATED IMAGING ABNORMALITIES (ARIA)

Solanezumab did not meet its primary end point, the change in score from baseline to week 80 on the ADAS-Cog11, in two phase III trials, EXPEDITION 1 AND EXPEDITION 2. But in EXPEDITION 2, a significant treatment effect was found in patients with mild AD (defined as MMSE score 20-26 at baseline) for the change in score in the ADCS-ADL scale, while in patients with moderate AD (defined as baseline MMSE score 16-19), a significant treatment effect was found for the change in the MMSE score (both $p = 0.04$) [31]. 17% of patients in EXPEDITION 1 and 9% of patients in EXPEDITION 2 underwent baseline and follow-up PET imaging of Aβ. The "composite standardized uptake value ratio" for PET-detectable Aβ in multiple AD pathology-containing brain regions (normalized to values for cerebellum) showed no significant changes in Solanezumab-treated or placebo-treated subjects in either study [31]. Among the subjects who underwent Aβ PET imaging, the rates of ARIA were similar between Solanezumab- and placebo-treated patients, for both ARIA with edema/effusion (ARIA-E) and ARIA with hemorrhage/hemosiderin deposition (ARIA-H). A subsequent phase III trial with Solanezumab which was limited to patients with mild AD with evidence of cerebral Aβ deposition (based on PET scan or CSF $A\beta_{1\text{-}42}$ measurement) did not meet its primary end point, which was the change from baseline to week 80 in ADAS-Cog14 [226, 227].

The effects of Aducanumab on patients with early AD were examined in two phase III trials, EMERGE and ENGAGE. "Early AD" was defined as MCI due to AD, or mild dementia due to AD; the presence of amyloid pathology was confirmed by PET. Inclusion criteria included MMSE score between 24-30 and Clinical Dementia Rating Scale (CDR) global score of 0.5. The primary outcome measure

for both studies was the CDR-sum of boxes (CSR-SB) score. Study arms included titrating to both low-dose and high-dose Aducanumab and were stratified by *APOE* status; low-dose Aducanumab was titrated to 3 mg/kg in *APOE4* carriers and 6 mg/kg in *APOE4* non-carriers, while high-dose Aducanumab was titrated to 6 mg/kg in *APOE4* carriers (subsequently revised to 10 mg/kg) and 10 mg/kg in *APOE4* non-carriers. Both trials were terminated based upon findings of a prespecified futility analysis performed after approximately 50% of the study subjects completed (or had the opportunity to complete) week 78 of the trials. The results of the trials were published by Biogen [33], which contended that some of the assumptions on which the futility analysis was based had been violated. Biogen announced that their analysis of a larger data set indicated that in EMERGE, the primary end point had been met with high-dose Aducanumab. A difference of -0.39 between high-dose Aducanumab and placebo in the mean change from baseline in CDR-SB score at week 78 had been found ($p = 0.012$), indicating a 22% reduction in the rate of cognitive decline. Positive results were also reported for the EMERGE high-dose arm on the three secondary end points, namely mean change from baseline at week 78 for MMSE ($p = 0.049$), ADAS-Cog13 ($p = 0.010$), and Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory-Mild Cognitive Impairment (ADCS-ADL-MCI) scores ($p < 0.001$). In contrast, in the ENGAGE trial, high-dose Aducanumab did not meet its primary or secondary end points. PET data from both studies showed "dose- and time-dependent reduction" in PET-detectable Aβ; the effect was statistically significant in both studies although the effect for high-dose Aducanumab at 78 weeks was 16.5% less in ENGAGE than in EMERGE. For patients treated with high-dose Aducanumab, a decrease in PET-detectable Aβ to the threshold level suggested to distinguish between Aβ-positive and Aβ-negative patients was reached by week 78 in 48% of EMERGE patients and 31% of ENGAGE patients. The incidence of ARIA-E for high-dose Aducanumab was 35% in EMERGE and 36% in ENGAGE, versus 2% and 3% for placebo-treated subjects, respectively. In both studies the incidence of ARIA-E was higher with high-dose Aducanumab than with low-dose Aducanumab, and higher in *APOE4* carriers than in *APOE4* non-carriers. (In pooled data from both studies the incidence of ARIA-E with high-dose Aducanumab was 65% in *APOE4* homozygotes and 35% in *APOE4* heterozygotes.) Subjects with ARIA-E were more likely than those without ARIA-E to have brain microhemorrhages and localized superficial siderosis (ARIA-H). The incidence of brain microhemorrhage for subjects treated with high-dose Aducanumab was 20% in EMERGE and 19% in ENGAGE, versus 7% and 6% for placebo-treated subjects. Localized superficial siderosis was noted for high-dose Aducanumab in 13% of EMERGE subjects and 16% of ENGAGE subjects, versus 3% and 2% for placebo-treated subjects.

A phase IIb trial, BAN2401-G000-201, was performed with Lecanemab. The effects of three doses of the antibody were evaluated across two regimens (administration monthly and bi-weekly) in patients with mild AD, including MCI attributable to AD. The findings were published by Eisai [35]. The primary end point, Bayesian analysis of change at 12 months on the Alzheimer's Disease Composite Score (ADCOMS) for the ED90 dose, was not met, but because conditions were not satisfied for terminating the trial based on futility analysis the trial continued for the full 18 months. A dose-dependent reduction of PET-detectable Aβ was found at 18 months, and in the study cohort receiving the highest dose of Lecanemab (10 mg/kg) twice monthly, statistically significant slowing of cognitive impairment (based on ADCOMS and ADAS-Cog14 scores; 30% and 47% slowing, respectively) was detected at 18 months.

An 18-month phase III trial with Lecanemab, Clarity AD, was subsequently performed, with the primary end point the change from baseline at 18 months in the CDR-SB score. Study subjects had MCI due to AD, or mild AD based on NIA-Alzheimer's Association criteria [228]. The results were published in November 2022 by van Dyck et al. [36]. The primary end point was met; 27% slowing of cognitive decline was achieved in Lecanemab-treated versus placebo-treated subjects ($p < 0.001$). van Dyck et al. noted that while there was no established definition for "clinically meaningful" effects in the CDR-SB score, the prospectively defined target had been exceeded. (Whether Lecanemab's effect in this study was clinically meaningful has been questioned [229]). Significant differences between Lecanemab-treated and placebo-treated subjects were also found for PET-detectable Aβ. Mean PET-Aβ at baseline for Lecanemab-treated and placebo-treated subjects were 77.92 centiloids (CTL) and 75.03 CTL, respectively; the adjusted mean change from baseline at 18 months was -55.48 CTL for Lecanemab-treated subjects versus 3.64 CTL for placebo-treated subjects ($p < 0.001$). (In a study comparing PET-

detectable and neuropathologically detectable Aβ in AD patients, CTL values greater than 20 were found to indicate at least moderate plaque density, while CTL < 10 reflected absence of neuritic plaques [230], so the mean detectable PET-Aβ in Lecanemab-treated subjects at 18 months approached the lower level of detection of moderate plaque density. The paper by van Dyck et al. [36] in which the Clarity AD results were published cited an older PET study, by Fleisher et al. [231], in which > 30 CTL was considered to represent elevated brain amyloid levels.) Secondary end points were also met in Clarity AD for measures of cognition, namely ADAS-cog14, ADCOMS, and ADCS-MCI-ADL (all $p < 0.001$). The incidence of ARIA-E in Lecanemab-treated and placebo-treated subjects was 12.6% and 1.7%, respectively, and the incidence of ARIA-H in Lecanemab-treated and placebo-treated subjects was 17.3% and 9.0%, respectively.

In Donanemab's phase II study TRAILBLAZER-ALZ, the primary end point was change from baseline at 76 weeks in the Integrated Alzheimer's Disease Rating Scale (iADRS), which assesses both cognitive and functional abilities [232]. Secondary measures included PET detection of Aβ and tau (the latter measured via ^{18}F-flortaucipir) and multiple measures of cognitive functioning. Findings were reported by Mintun et al. [233]. The primary end point was achieved, with 32% slowing of decline in Donanemab-treated versus placebo-treated subjects as measured by iADRS ($p = 0.04$), although no statistically significant differences between treatment and placebo groups were found for CDR-SB scores, a secondary measure of cognition. Topline results were released by Lilly on May 3, 2023 for Donanemab's phase III trial TRAILBLAZER-ALZ 2 [37], whose study subjects were individuals with MCI or early AD. The selection process for study participants included cognitive testing and PET screening for brain levels of insoluble Aβ and tau. The primary end point in TRAILBLAZER-ALZ 2 was change from baseline to 18 months on the iADRS. Subjects included in the primary analysis had intermediate levels of insoluble tau. As stated earlier the primary end point was met, as were all secondary end points (CDR-SB, Alzheimer's Disease Cooperative Study - instrumental Activities of Daily Living Inventory [ADCS-iADL], and the ADAS-Cog13). Relative slowing on the iADRS of Donanemab-treated subjects with intermediate tau levels was 40% based on one statistical analysis and 35% based on another analysis. Slowing of disease progression in the "intermediate tau level" subjects based upon the scales assessed in the secondary end points was similar to that for the iADRS. When the analysis included subjects with high tau levels as well as those with intermediate tau levels, Donanemab was less effective at slowing AD progression, based upon iADRS scores (23% and 22% relative slowing as assessed by the two statistical procedures) although the differences versus placebo were still highly statistically significant (p values < 0.00004 and < 0.00006). Donanemab was effective at lowering brain levels of PET-detectable Aβ, with 34% of subjects in the primary analysis reported to achieve plaque clearance by 6 months and 71% achieving this goal by 12 months. ARIA-E and ARIA-H were detected in 24% and 31% of Donanemab-treated subjects, respectively. (The topline results did not include the incidence of ARIA-E in placebo-treated subjects; the incidence of ARIA-H in these subjects was reported to be 13.6%). Although most cases of ARIA were rated as mild-to-moderate, two deaths in TRAILBLAZER-ALZ 2 were attributed to ARIA, and another subject died after an incident of serious ARIA. Lilly's announcement of its topline results included a statement that the company will proceed with submissions of regulatory approval for Donanemab in the United States and globally.

SIGNIFICANCE OF ANTI-Aβ MONOCLONAL ANTIBODY-ASSOCIATED ARIA

As discussed above, treatment of AD patients with Aducanumab, Lecanemab, and Donanemab increased the incidence of ARIA, and other monoclonal antibodies targeting Aβ's N-terminal amino acids, including Bapineuzumab and Gantenerumab, also increased the incidence of ARIA [234–239]. The mechanisms underlying ARIA are incompletely understood. The development of ARIA in the anti-Aβ monoclonal antibody trials was suggested to be due to increased production of inflammatory cytokines secondary to antibody-induced activation of microglia [217, 240, 241]. The Alzheimer's Association Research Roundtable Workgroup [242] suggested that the increased incidence of ARIA in Bapineuzumab-treated subjects might be related to increased clearance of plaque-associated Aβ, causing a transient elevation in the cerebrovascular level of Aβ, which could increase vascular fragility and permeability.

Treatment-associated ARIA-E is usually short-lived and may be clinically asymptomatic [234, 235]. Spontaneous development of ARIA-E is rare, although its incidence increases in individuals with CAA and in *APOE4* carriers [239, 242]. ARIA-H indicates the presence of cerebral microhemorrhages (microbleeds), which are classified according to their location as either lobar or deep microbleeds. Lobar microbleeds may be located in the cortex ("lobar cerebral microbleeds"), gray-white matter junction, subcortical white matter, or cerebellum ("lobar cerebellar microbleeds"), while deep microbleeds are present in basal ganglia gray matter, internal/external capsules, thalamus, or brain stem [221]. A community-based study found that cerebral microbleeds may be present by middle age and their incidence increases with age [243]. Lobar microbleeds have been reported to be an indicator of CAA [244], whereas combined lobar and deep microbleeds may be due to hypertensive angiopathy or atherosclerosis [221, 245]. The incidence of lobar microbleeds is increased in *APOE4* carriers [245, 246].

It is not clear if microbleeds adversely affect cognitive performance [247]. Studies of community-based individuals without dementia have associated an increased incidence of microbleeds with lower cognitive functioning and increased risk for dementia [248–251]. Conflicting reports have been published as to the association between microbleeds and cognitive performance in AD patients. Some studies have not found associations between these factors [247, 252, 253], but a study comparing MMSE scores between AD patients with multiple cerebral microbleeds and AD patients without microbleeds found that the patients with multiple microbleeds had lower MMSE scores despite similar duration of clinical disease [254].

In three Bapineuzumab phase II trials, 49% of the patients who developed ARIA-E also developed ARIA-H, suggesting a common mechanism for the two types of ARIA [255]. In those trials, although some patients with ARIA-E were asymptomatic, in other patients ARIA-E was associated with headache, confusion, visual disturbances, and gait abnormalities [242]. Similar adverse effects, plus nausea, were reported in subjects in the Aducanumab phase III trials who developed ARIA-E [256]. The increased risk for ARIA is a concern with regard to the use of N-terminal targeting anti-Aβ monoclonal antibodies for treatment of AD.

Some of the anti-Aβ monoclonal antibodies evaluated in clinical trials were designed to limit the development of ARIA. Crenezumab's isotype is IgG4, which binds less avidly than IgG1 to the microglial FcR and does not induce microglial activation [241]. Ponezumab contains two mutations in its Fc region, inactivating this part of the antibody and preventing it from activating complement or triggering antibody-dependent cell-mediated cytotoxicity [206]. Deglycosylation of anti-Aβ antibodies has also been suggested as an approach to limit antibody-driven inflammation, because deglycosylation reduces the affinity of antibody binding to the FcR and to complement [257].

DOWNSTREAM EFFECTS OF ANTI-Aβ ANTIBODIES IN CLINICAL TRIALS

According to the amyloid hypothesis a number of pathological conditions occur between increased Aβ aggregation (or, in the revised hypothesis, the formation of Aβ oligomers) and the development of dementia. These include tau pathology, cell loss, and vascular damage [5], and possibly other conditions including oxidative stress, inflammation, mitochondrial dysfunction, and impaired autophagy. It is unclear which if any of these downstream processes are appropriate therapeutic targets. Even if some monoclonal anti-Aβ antibodies are able to slow AD progression (as Lecanemab and Donanemab have been shown to do), targeting of other factors in addition to Aβ may be required to further slow the disease [258].

Biomarkers for downstream events that have been evaluated in AD trials involving Aβ vaccination, IVIG, and monoclonal anti-Aβ antibodies include CSF concentrations of total tau (t-tau), phosphorylated tau (p-tau), neurofilament light chain (NfL), neurogranin, interleukin-6 (IL-6), α-synuclein, glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B), soluble triggering receptor expressed on myeloid cells 2 (sTREM2), and chitinase-3-like protein 1 (YKL-40), as well as tau PET imaging. In some of the clinical trials statistically significant differences in the levels of these biomarkers were found between the treatment and placebo groups despite no evidence of lowering of PET-detectable Aβ; in those trials the mechanism responsible for the changes in the downstream markers is unknown. The significance of CSF t-tau measurements in AD is controversial. CSF t-tau levels are increased in some, but not all, AD patients [259, 260]; increased CSF t-tau was reported to be

associated with dysregulation of neuronal plasticity, whereas AD subjects lacking evidence for dysregulated neuronal plasticity (i.e., AD subjects with lower CSF levels of neuronal plasticity proteins) had normal CSF concentrations of t-tau [261]. CSF p-tau, including p-tau-181, p-tau-217, and p-tau-231, is also increased in AD patients [262], although CSF p-tau-181 was reported to decrease in later stages of AD [263]. Hyperphosphorylation of tau causes sequestering of normal tau, leading to microtubule disassembly. This compromises axoplasmic flow, initially causing synaptic loss and ultimately resulting in neurodegeneration [264, 265]. NfL is a scaffolding protein of the neuronal exoskeleton whose CSF concentration increases with axonal damage [266], so it is considered to be a biomarker for axonal damage and neurodegeneration [267, 268]. CSF NfL increases during normal aging and AD [266] and is positively associated with AD progression [269–271], increased ventricular volume [270], and hippocampal atrophy [272]. Neurogranin is a postsynaptic protein involved in long-term potentiation signaling [273] and is thought to play a major role in regulating hippocampal synaptic plasticity and synaptic function [274]. Neurogranin concentrations are decreased in AD brain and increased in AD CSF, and it has been suggested to be a marker for synaptic dysfunction or synaptic loss [275–277]. IL-6, a pro-inflammatory cytokine, is a biomarker for inflammation [278]. α-synuclein is the main component of Lewy bodies and is a biomarker for Parkinson's disease and other synucleinopathies [279]. GFAP is a cytoskeletal component of reactive astrocytes [280]. S100B is another astrocytic protein which has been used as a biomarker for neurodegeneration [281]. sTREM2 is the soluble form of TREM2, which is expressed in the CNS mainly on microglia [282] and is a biomarker for microglial activation [283]. YKL-40 is an astrocyte-derived biomarker involved in inflammation, proliferation, and angiogenesis [284].

In the AN1792 vaccination trial, CSF t-tau was measured in a small subset of the study subjects. It was significantly decreased ($p < 0.001$) in antibody responders ($n = 11$) compared to placebo (saline) - treated patients ($n = 10$) [23]. The significance of this finding was uncertain because postmortem studies on some of the study subjects indicated that tau pathology did not appear to be affected by Aβ vaccination [177, 184–186].

In the phase II trial with the IVIG preparation Octagam [28], no significant changes versus placebo were found for CSF t-tau or p-tau-181. A similar result was found in the phase III trial with the IVIG product Gammagard [29]. Interestingly, in a study of the effects of Gammagard in 3xTg mice, hippocampal neurofibrillary tangle pathology was found to be decreased by 25-30% [285]. It was unclear if this was a downstream effect of Gammagard's anti-Aβ antibodies, because as stated above some IVIG products also contain antibodies to non-phosphorylated tau and p-tau (p-tau-199 and p-tau-202) [154, 155]. Gammagard was found in another study to impair *in vitro* tau aggregation [286].

Two phase III trials, one with *APOE4* carriers and the other with *APOE4* non-carriers, were performed with Bapineuzumab in AD patients, because of the finding in a phase II trial of possible differences in antibody efficacy and the incidence of vasogenic edema between *APOE4* carriers and non-carriers in Bapineuzumab-treated subjects [287]. CSF p-tau (phosphorylation site not stated) was measured in both trials. The results of the trials were published by Salloway et al. [32]. A significant difference for CSF p-tau concentration between Bapineuzumab-treated and placebo-treated subjects (reflecting decreased CSF p-tau in Bapineuzumab-treated subjects) was found in the *APOE4* carrier study. In the *APOE4* non-carrier study, no significant difference was found for CSF p-tau between the pooled 0.5 mg/kg Bapineuzumab and 1.0 mg/kg Bapineuzumab groups, although a pre-specified exploratory analysis found lower p-tau in the 1.0 mg/kg Bapineuzumab-treated group than in the placebo group. The decrease in CSF p-tau in Bapineuzumab-treated *APOE4* carriers could have been a downstream effect of reduced cerebral Aβ because in that study, the mean change in PET-detectable Aβ was significantly different between treated and placebo subjects ($p = 0.004$) for the 0.5 mg/kg Bapineuzumab dose. In contrast, no significant differences were seen for PET-detectable Aβ between Bapineuzumab-treated and placebo-treated subjects in the non-*APOE4* carrier trial.

In the first two phase III trials with Solanezumab, CSF t-tau and p-tau-181 were measured in a subset of the study subjects. No significant changes in these biomarkers were found in either Solanezumab-treated or placebo-treated patients in either study [31]. The effects of Solanezumab, together with those of the anti-Aβ monoclonal antibody Gantenerumab (discussed below), were also evaluated in a prevention study, DIAN-TU-001, performed by the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU). Study subjects carried mutations associated with early-onset AD and were asymp-

tomatic or mildly symptomatic. The study evolved from a phase II biomarker trial to a phase III cognitive end point trial. Solanezumab treatment did not change CSF t-tau or p-tau concentrations in the study subjects; however, it produced an unexpected, statistically significant increase in CSF NfL concentrations at year 4 of the study. Whether this was due to an increase in disease progression, a problem with the study design, or some other factor was not determined [288, 289].

Several clinical trials have been performed with Gantenerumab. Scarlet RoAD was a phase II study in patients with prodromal AD (MCI thought to be due to AD [290, 291]) and Marguerite RoAD was a phase III trial in patients with mild AD [292]. Both trials were terminated based on findings from futility analyses. Downstream biomarkers examined in a subset of patients in Scarlet RoAD included CSF t-tau, p-tau-181, and neurogranin. Exploratory analyses suggested dose-related lowering of all three biomarkers [237]. In Marguerite RoAD, CSF t-tau and p-tau-181 decreased from baseline in Gantenerumab-treated subjects compared to placebo-treated subjects at 52 and 104 weeks ($p = 0.053$ for p-tau-181 at week 104) [293]. In year 4 of the DIAN-TU-001 preventative trial, CSF t-tau and p-tau-181 were lower in Gantenerumab-treated subjects than in placebo-treated subjects (both $p < 0.001$), and the increase in CSF NfL concentration was less in Gantenerumab- treated subjects than in placebo-treated subjects ($p < 0.05$) [289].

Ponezumab was intended to bind to, and sequester, Aβ in peripheral blood, with the hope that it would lower cerebral Aβ via the peripheral sink mechanism [206]. But as discussed above, phase II studies with Ponezumab found no effects on CSF Aβ, and CSF t-tau and p-tau (phosphorylation site not stated) were also unchanged [207, 294].

Crenezumab's efficacy in AD patients was examined in two phase II trials, BLAZE and ABBY [295, 296]. Crenezumab failed to meet primary end points, and it did not appear to influence CSF t-tau or p-tau-181 levels, in either trial. Crenezumab was further evaluated in two phase III trials, CREAD and CREAD2, both of which were terminated due to futility analysis [297]. Similar to the phase II trials, no evidence was found in Crenezumab's phase III trials for treatment-related changes in CSF t-tau or p-tau-181. In CREAD2, PET-detectable tau was measured at baseline and 53 weeks. An unexpected increase in PET tau ($p = 0.03$) was found in the Crenezumab-treated subgroup at 53 weeks. Exploratory analyses of changes from baseline were performed on other CSF biomarkers (pooled data from CREAD and CREAD2) including Aβ oligomers, neurogranin, NfL, IL-6, α-synuclein, GFAP, S100B, sTREM2, and YKL-40. These analyses suggested lowering of neurogranin, NfL, α-synuclein, GFAP, sTREM2, and YKL-40 at week 105 in Crenezumab-treated subjects compared to placebo-treated subjects. However, the only biomarker which achieved clear separation (as indicated by no overlapping of standard error bars) was neurogranin, whose CSF concentration was unchanged at weeks 53 and 105 in placebo-treated subjects but decreased in Crenezumab-treated subjects at week 53, with a further decrease at week 105.

Crenezumab was also administered to subjects in the Alzheimer's Prevention Initiative (API) Colombian trial, a phase II trial which investigated its safety and efficacy in non-cognitively impaired carriers of the E280Q presenilin 1 mutation. The study also included a placebo-treated non-carrier cohort. Topline results revealed no evidence of a significant clinical benefit in either of the study's primary end points, which assessed the rate of change in cognitive abilities and episodic memory function [298]. CSF t-tau, p-tau (phosphorylation site not stated), and NfL levels were lowered in Crenezumab-treated subjects by 29%, 37%, and 18% compared to placebo-treated subjects, but these differences were not statistically significant [299, 300].

CSF and PET studies performed on subsets of study subjects in Aducanumab's two phase III trials [33] suggested that the highest dose of Aducanumab slowed the development of tau pathology. CSF t-tau and p-tau-181 were measured at baseline and week 78, and tau PET imaging was performed at screening and week 78. Dose-dependent reductions in CSF total and p-tau-181 were found in one study, while in the other study these measures decreased only in the high-dose group. Pooled results from the two studies indicated that the highest dose of Aducanumab reduced PET-detectable tau in medial temporal, temporal, and frontal lobes.

In Lecanemab's phase IIb trial [35], CSF studies (collected at baseline, 12 months, and 18 months) included measurements of t-tau, p-tau (phosphorylation site not stated; probably p-tau-181, because Lecanemab's phase III trial, discussed below, measured p-tau-181), neurogranin, and NfL. The least squares mean difference for p-tau was decreased in Lecanemab- versus placebo-treated subjects, but findings for t-tau were inconsistent. Neurogranin was

significantly decreased in Lecanemab-treated versus placebo-treated subjects at 12 months but not at 18 months, while differences for NfL between Lecanemab-treated and placebo-treated patients were not significant at either time point. Lecanemab's phase III trial [36] included measurements of PET-detectable tau and CSF t-tau, p-tau-181, neurogranin, and NfL. Prespecified analyses found "numerical improvements" between Lecanemab-treated and placebo-treated subjects for the CSF biomarkers other than NfL. The tau PET results were reported to have not been fully analyzed, although topline results mentioned that Lecanemab treatment slowed the development of tau pathology (based on PET detection of tau) in the temporal lobe [301].

In Donanemab's phase II study TRAILBLAZER-ALZ, prespecified analyses presented at the International Conference on Alzheimer's and Parkinson's Diseases 2021 [302] and the Alzheimer's Association International Conference 2021 [303] indicated that Donanemab reduced development of tau pathology in frontal, parietal, and lateral temporal lobes. Lilly's announcement in May 2023 of topline results for Donanemab's phase III trial TRAILBLAZER-ALZ 2 [37] did not mention downstream effects. The ClinicalTrials.gov posting for TRAILBLAZER-ALZ 2 [304] states that one of the secondary outcome measures in the study is change from baseline in PET-detectable tau. This result will likely be reported at the Alzheimer's Association International Conference in July 2023.

Some of the antibodies which produced detectable downstream effects targeted Aβ conformations other than oligomers (Donanemab targeted Aβ fibrils) or other Aβ conformations in addition to oligomers (Bapineuzumab bound to Aβ monomers, oligomers, and fibrils, Gantanerumab bound to Aβ oligomers and fibrils, Aducanumab bound to oligomers and fibrils, and Lecanemab bound to protofibrils and fibrils as well as oligomers). This suggests that while antibody targeting of oligomeric Aβ may be optimal, because oligomers are thought to be the most neurotoxic Aβ conformation [305], effective targeting of other Aβ conformations can also decrease downstream pathological processes, even if significant slowing of cognitive decline is not achieved. An unanswered question is whether AD's clinical progression can slowed by directly targeting downstream pathological mechanisms. The first clinical trials of anti-tau monoclonal antibodies in AD failed to meet their primary end points [306–309]. Nonsteroidal anti-inflammatory agents (NSAIDs) [310–314] and the peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists rosiglitazone [315, 316] and pioglitazone [317] also failed to meet primary end points in large-scale clinical trials, while trials with antioxidants produced mixed results [318–321]. Future AD trials with anti-Aβ monoclonal antibodies should assess treatment-associated changes in CSF levels of Aβ oligomers, as well as changes in downstream biomarkers including PET-detectable tau and CSF t-tau, p-tau, and inflammatory and oxidative stress proteins. Determining the downstream effects of anti-Aβ monoclonals is important because the ability of these antibodies to slow AD progression may depend on the extent to which they reduce downstream pathological processes.

POTENTIAL APPROACHES TO INCREASE THE ABILITY OF MONOCLONAL ANTI-Aβ ANTIBODIES TO SLOW AD PROGRESSION

The results for the phase III trials with Aducanumab, Lecanemab, and Donanemab indicate that treatment of AD patients with these antibodies can efficiently reduce brain levels of PET-detectable (insoluble) Aβ. High-dose Aducanumab reduced PET-Aβ to threshold levels in 48% of subjects in EMERGE and 31% of patients in ENGAGE [33], while in Lecanemab's Clarity AD trial the mean detectable level of PET-Aβ in antibody-treated subjects approached the lower limit for detection of moderate plaque density [36], and in Donanemab's TRAILBLAZER-ALZ 2, PET-Aβ was cleared in 71% of subjects in the primary analysis group (subjects with intermediate brain levels of insoluble tau) [37]. The finding that this lowering of insoluble Aβ was associated with slowing of disease progression (high-dose Aducanumab slowed cognitive decline by 22% in EMERGE, Lecanemab slowed cognitive decline by 27% in Clarity AD, and Donanemab slowed cognitive decline by 35-40% in TRAILBLAZER-ALZ 2) provides the strongest support yet for the amyloid hypothesis. As mentioned above, the question has been raised for Lecanemab as to whether its slowing of cognitive decline (a mean difference of 0.45 points on CDR-SB) is clinically meaningful [229]. The same question can be asked for Donanemab. Given that the antibodies (particularly Lecanemab and Donanemab) are effective at reducing PET-detectable Aβ, are the rates of slowing of cognitive decline achieved in their phase III trials

the maximum that can obtained by antibody targeting of Aβ alone?

Several approaches could be considered in an effort to increase the ability of these antibodies to slow AD progression. Antibody-facilitated microglial degradation of Aβ might be increased by preventing, or at least decreasing, the shift in microglial activation phenotype from M2 (anti-inflammatory) to M1 (pro-inflammatory) which is thought to occur during AD progression [54–57]. NSAIDs, pioglitazone, rosiglitazone, and curcumin are agents which have been suggested to promote glial cell M2-type activation [322–326]. Increasing the expression and/or activity of microglial enzymes which degrade Aβ such as neprilysin, insulin-degrading enzyme, tissue plasminogen activator, cathepsin B, and matrix metalloproteinases [327] might also increase antibody-facilitated clearance of Aβ by microglia. In addition, enhancing the other mechanisms by which antibodies promote cerebral clearance of Aβ might enhance the ability of monoclonal antibodies to lower brain Aβ. For example, increasing the expression of LRP1 or the neonatal FcR on BBB endothelial cells might increase efflux of antibody-Aβ complexes from the brain through binding of antibody-Aβ complexes to these receptors. Increasing the ability of the monoclonal antibodies to enter the brain (possibly through the use of focused ultrasound, as was used in an experimental study with IVIG [163]) might also improve the antibodies' Aβ-clearing ability. Finally, administration of an antibody such as Lecanemab, which targets soluble Aβ (protofibrils are large soluble oligomeric species [328, 329]), combined with an intervention designed to increase peripheral sink efflux of Aβ from the brain, is another approach that could be considered. Approaches that may increase peripheral sink efflux of brain Aβ include plasmapheresis with albumin replacement as was done in the AMBAR study [38, 39], administration of a monoclonal antibody designed to sequester peripheral blood Aβ by binding to its C-terminal residues (although the Aβ C-terminal-binding antibody Ponezumab failed to lower brain Aβ in phase II trials [207], and increasing peripheral blood levels of sLRP1. LRP1 is the main receptor mediating Aβ efflux from the brain into the peripheral circulation via the BBB [330, 331]; cleavage of LRP1 on cell surfaces results in shedding of sLRP1 into plasma [112]. sLRP1 binds 70% of plasma $A\beta_{40}$ and 90% of plasma $A\beta_{42}$ in neurologically normal subjects, with lower binding in AD patients [111].

As discussed above, the development of ARIA is a concern when AD patients are treated with approaches which mobilize brain Aβ. In the anti-Aβ monoclonal antibody trials, many of the cases of ARIA were asymptomatic. In Aducanumab's phase III trials EMERGE and ENGAGE, approximately one-third of Aducanumab-treated patients developed ARIA-E, with only a quarter of these being symptomatic [332] and in Donanemab's phase III trial TRAILBLAZER-ALZ 2, ARIA-E developed in 24% of Donanemab-treated patients, but it was symptomatic in only 6.1% of the Donanemab-treated patients [37]. However, ARIA can have serious clinical consequences. It would be worthwhile to determine if either Lecanemab or Donanemab can be modified to reduce its ability to induce ARIA, while retaining its ability to slow AD progression. The development of microhemorrhages and microglial activation can be prevented when anti-Aβ antibodies targeting N-terminal epitopes of Aβ are deglycosylated [333].

Finally, while recent clinical trials with AD patients have been limited to individuals with early AD (including MCI attributed to AD), there is an urgent need to develop therapies which can slow progression of patients who are in later stages of the disease. Even if targeting of Aβ by some monoclonal antibodies is effective at slowing the progression of early AD, it is unclear if this approach will be beneficial in later stages of AD. At some point in the disease process, downstream pathological processes may continue irrespective of treatment-induced reductions in brain Aβ.

CONCLUSIONS

To date, the only anti-Aβ monoclonal antibodies which have unequivocally been shown to slow AD progression are Lecanemab and Donanemab. Whether the effects of these antibodies on AD progression are also clinically meaningful is unclear. Antibodies promote clearance of Aβ from the brain by multiple mechanisms, offering possibilities for increasing this process. The extent to which antibodies which target Aβ are able to slow the progression of early AD may depend not only on their ability to reduce brain levels of Aβ aggregates, but also on their ability to decrease downstream pathological processes. Designing of future anti-Aβ monoclonal antibodies should include efforts to minimize the ability of these antibodies to induce ARIA.

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CONFLICT OF INTEREST

The author has no conflict of interest to report.

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