



Available online at <https://s-epub.in/index.php/trp/index>

Pharma Research

An International Peer Reviewed, Indexed Journal

[10.62655/s-epub.2026.v18.i01.pp95-104](https://s-epub.in/index.php/trp/index)

ANTI-AMYLOID MONOCLONAL ANTIBODIES IN EARLY ALZHEIMER'S DISEASE: BENEFITS AND SAFETY SIGNALS

EMILY DUNLEAVY^{1*}, RACHEL FAIRBANKS², TREVOR MERRIWEATHER²

Affiliation

¹Department of Pharmacology, Shenandoah Valley College of Pharmacy, Harrisonburg, USA

²Department of Experimental Pharmacology, Shenandoah Valley College of Pharmacy, Harrisonburg, USA

*Corresponding author: Emily Dunleavy, e.dunleavy@svcp.edu

ORCID iD: Emily Dunleavy 0000-0001-2420-2748; Rachel Fairbanks 0000-0001-2883-7281; Trevor Merriweather 0000-0001-4412-0248

Article info

Received date:07-06-2025

Accepted date:15-10-2025

Published date:18-02-2026

ISSN;0975-8216

Keywords:

Alzheimer's disease, Monoclonal antibodies, Amyloid- β , Lecanemab, Donanemab

1. INTRODUCTION

Alzheimer's disease is the commonest cause of dementia, and for most of the past century treatment meant managing symptoms. Cholinesterase inhibitors and memantine ease cognitive and functional decline modestly and for a limited time, but they leave the underlying pathology untouched. The amyloid cascade hypothesis, set out in 1992, proposed that accumulation of amyloid- β (A β) is the initiating event, with tau pathology, synaptic loss and neuronal death following downstream [1]. Three decades of work have refined the idea rather than

Abstract

Anti-amyloid monoclonal antibodies are the first disease-modifying treatments to show a measurable slowing of clinical decline in early Alzheimer's disease. This review, which reports no new data, summarises the published literature on the amyloid rationale, the earlier antibodies that failed, the main trials of aducanumab, lecanemab and donanemab, and the safety signals that accompany them, above all amyloid-related imaging abnormalities. Benefits are real but modest in absolute terms, and they depend on careful biomarker-based selection and regular MRI monitoring. Safety risks are higher in carriers of the APOE ϵ 4 allele. Evidence beyond 18 months, in diverse populations and against alternative strategies is still lacking, and practical delivery poses serious problems for health services.

abandoned it, and the hypothesis has been tested most directly by antibodies designed to remove A β from the brain [2, 3]. Their results, good and bad, now shape how the

field thinks about disease modification, and they are discussed here with particular attention to the size of the effects and the cost in safety terms.

The treatment target is early disease. In current frameworks this means mild cognitive impairment or mild dementia with biomarker evidence of amyloid pathology, established by positron emission tomography (PET) or cerebrospinal fluid testing [4, 5]. The biological definition of Alzheimer's disease has itself been revised more than once, and the most recent proposals again put amyloid and tau biomarkers at the centre while staging disease by clinical and biological features [6]. These definitions matter for trials, because enrolling people who do not have amyloid pathology dilutes any treatment effect, and they matter for practice, because eligibility for these drugs depends on confirming that the pathology is there before treatment starts.

This review brings together the published evidence on anti-amyloid antibodies in early Alzheimer's disease, covering the target and its biomarkers, the earlier trials that did not succeed, the main trials of the agents that have shown benefit, the safety signals, and what all this means for practice. It reports no new data. The aim is to describe what the trials found and how far the findings can be pushed, without overstating either the benefits or the harms. Regulatory decisions have differed between countries and are mentioned only where they bear on how the evidence has been interpreted [7, 8].

2. AMYLOID AS A TREATMENT TARGET

The case for A β rests on several lines of evidence that point the same way. Mutations in the amyloid precursor protein gene and in the presenilin genes, which alter A β production, cause early-onset familial Alzheimer's disease, and people with Down syndrome, who carry an extra copy of the precursor gene, develop amyloid pathology early [2]. The ϵ 4 allele of the apolipoprotein E gene, the strongest common genetic risk factor for late-onset disease, increases risk in a dose-dependent way and is linked to earlier and heavier amyloid deposition [9]. Critics point out that plaque burden correlates only

loosely with symptoms in individual patients, which is true, but the genetic data make a causal role for A β difficult to dismiss [3].

A β is not a single target. The peptide exists as monomers, soluble oligomers, protofibrils, insoluble fibrils and plaques, and some of these forms appear more toxic than others, with soluble oligomers able to disturb synaptic function in experimental systems [10]. Antibodies differ in what they bind. Solanezumab was designed to recognise monomeric A β , while aducanumab and gantenerumab prefer aggregated forms, lecanemab binds protofibrils with high affinity, and donanemab recognises a pyroglutamate-modified form that is found only in established plaques [11, 12, 13, 14]. These binding profiles are thought to account for differences in both efficacy and the pattern of side effects, although the link between binding profile and clinical effect remains an inference.

How the antibodies clear amyloid is still debated. The most accepted route involves antibody bound to deposited A β engaging Fc receptors on microglia, which then phagocytose the plaque, while an alternative proposal for monomer-binding antibodies is a peripheral sink that draws soluble A β out of the brain [3]. In early human work, aducanumab produced dose- and time-dependent reduction of plaques measured by PET, and later antibodies reached still higher rates of clearance [11, 13]. Plaque removal is quantified using standardised uptake value ratios or centiloids, and the proportion of participants whose scans fall below a threshold has become a surrogate endpoint. Its link to clinical benefit is plausible but incompletely established, as the gantenerumab experience shows [15].

Selecting the right patient depends on biomarkers. Amyloid PET shows plaque directly, and in a large US registry-based study of older adults with cognitive impairment, PET results changed clinical management in a substantial fraction of cases [16]. Cerebrospinal fluid A β 42 and phosphorylated tau serve the same purpose but need a lumbar puncture. Blood tests are advancing quickly, and plasma phosphorylated tau (p-tau217) discriminates

Alzheimer's disease from other neurodegenerative disorders with high accuracy in cohort studies, which raises the prospect of cheaper screening before confirmatory PET [17, 18]. For now, most centres use blood tests for triage and imaging or CSF for confirmation, as the reference standards remain those against which blood tests are judged [4, 6].

A recurring argument concerns whether Alzheimer's disease should be defined biologically, so that a person with a positive amyloid scan and no symptoms is already considered to have the disease, or clinically, so that the label applies only when symptoms appear. The research framework of 2018 took the first view, and critics argued that it risked labelling people with a condition they might never develop symptoms from [4]. The 2024 revision keeps biomarkers central but is more explicit about staging and about when biomarkers should and should not be used in clinical settings [6]. For treatment decisions, the practical point is simple: the drugs were tested in people with both symptoms and positive biomarkers, and there is no evidence yet to justify use outside that group.

3. EARLIER ANTIBODIES THAT FAILED

Before the recent successes came a long run of negative phase 3 trials. Bapineuzumab, the first antibody to reach late-stage testing, was studied in mild-to-moderate Alzheimer's disease in two large trials that found no benefit on cognition or function, despite some effect on biomarkers [19]. Vasogenic oedema, later termed ARIA-E, occurred in a dose-related way and was most frequent in APOE ϵ 4 carriers, so the safety signal now seen with modern antibodies was visible from the start [19]. Solanezumab, a monomer-binding antibody, had two parallel phase 3 trials that also failed their primary endpoints, although a pooled analysis in mild disease hinted at slowed decline, a hint that a later dedicated trial in mild dementia did not confirm [20, 21].

Crenezumab and gantenerumab followed the same path. Crenezumab, an IgG4 antibody with weak effector function that was thought to be safer in terms of ARIA, was tested in

two phase 3 trials in early disease and did not slow decline [22]. Gantenerumab is more interesting because it did lower amyloid on PET, in some participants to a large extent, yet the two phase 3 GRADUATE trials found no significant clinical benefit on the primary endpoint [15]. Possible explanations include dosing that was too low or too slow to clear plaque in time, and the fact that the amount of amyloid removed was lower than that reached with the later antibodies [3, 15].

Several lessons were drawn from this period. One was patient selection. In the early trials a meaningful proportion of participants clinically diagnosed with Alzheimer's disease had negative amyloid scans when these were eventually done, which meant that the antibody was being tested in some people who did not have the target [19, 20]. Another was stage, since mild-to-moderate dementia may be too late for removal of amyloid to alter the course. A third was exposure, which in several programmes was limited by the ARIA risk. Later programmes enrolled earlier disease, required biomarker confirmation and pushed dosing harder, and it is this redesign more than any change in the underlying idea that coincides with the later positive findings [3, 23].

Dose and regimen deserve a separate comment. Many of the early programmes used doses chosen largely for tolerability, and the biomarker readouts suggested that plaque reduction was partial and slow [15, 19]. Later programmes accepted a higher ARIA rate in return for greater amyloid lowering, using titration schedules in which the dose is raised stepwise to blunt early oedema [24, 25]. Pharmacokinetic features such as half-life, brain penetration and the fraction of antibody reaching the target are rarely reported, although they probably explain part of the variation in potency between antibodies. Better measurement of exposure, not just dose, would help to interpret why some antibodies cleared plaque and others did not [12, 14].

4. CLINICAL EVIDENCE FOR AGENTS THAT SHOWED BENEFIT

Aducanumab produced the most contested data. A phase 1b study showed

dose-dependent plaque reduction and a signal on clinical scales [11]. The two phase 3 trials, EMERGE and ENGAGE, were stopped early for futility and then, after additional data were analysed, were reported with discordant results: EMERGE showed less decline on the Clinical Dementia Rating Sum of Boxes (CDR-SB) in the high-dose arm, whereas ENGAGE did not [26]. The main and earlier trials are compared in table 1. Aducanumab received accelerated approval in the United States based on amyloid reduction as a surrogate endpoint, a decision that was widely criticised because the clinical evidence was inconsistent [7].

Table 1: Anti-amyloid antibody trials and evidence summarised in this review

Antibody or topic	Main published finding	Ref.
Bapineuzumab phase 3, mild to moderate	No clinical benefit; dose-related vasogenic oedema, most in APOE ε4 carriers	[19]
Solanezumab phase 3	Monomer-binding antibody; primary endpoints not met in mild to moderate or mild disease	[20, 21]
Crenezumab phase 3, early disease	No slowing of decline in two trials	[22]
Gantenerumab phase 3	Amyloid lowered on PET but no significant clinical benefit	[15]
Aducanumab phase 1b and 3	Plaque reduction; discordant phase 3 results; accelerated approval debated	[11, 26]
Lecanemab phase 2b and CLARITY AD	Marked amyloid clearance; 27% relative slowing on CDR-SB at 18 months	[12, 27]
Donanemab phase 2 and 3	Large plaque clearance; slowing greatest in low-to-medium tau group	[13, 24]
ARIA imaging and management	Oedema and microhaemorrhage linked to vascular amyloid; MRI monitoring advised	[28, 29]
Appropriate use eligibility	Biomarker confirmation, MRI screening and APOE counselling recommended	[30, 31]
Meta-analyses clinical importance	Small average benefit, increased ARIA, effects near or below thresholds	[32, 33]

Antibody or topic	Main published finding	Ref.
Plasma p-tau217 screening	High accuracy for Alzheimer's disease; may triage patients before PET	[17, 18]

Lecanemab has the clearest dataset. A phase 2b dose-finding study with Bayesian design supported the dose later chosen for phase 3 and showed marked reduction of PET amyloid [12]. CLARITY AD randomised about 1,800 people with early disease and confirmed amyloid to lecanemab 10 mg/kg every two weeks or placebo for 18 months. The change in CDR-SB was smaller with lecanemab, by 0.45 points, a relative slowing of about 27 per cent, and secondary measures of cognition, function and amyloid burden moved in the same direction [27]. Most treated participants had amyloid PET results below the positivity threshold at the end of the study, and the treatment effect appeared to grow over time rather than plateau.

Donanemab differs in its dosing logic. The phase 2 TRAILBLAZER-ALZ trial showed slowing on the integrated Alzheimer's Disease Rating Scale and a very large reduction of plaque, with a substantial number of participants reaching amyloid-negative scans [13]. The phase 3 TRAILBLAZER-ALZ 2 trial enrolled people with early symptomatic disease and used tau PET to define a primary population with low-to-medium tau [24]. In that group decline was slowed by roughly a third on the primary scale over 76 weeks, and a smaller benefit was found in the combined population including high tau. Dosing could be stopped once plaque had cleared, a time-limited approach that may reduce cost and exposure, but its long-term consequences have not been established [24].

Secondary and biomarker outcomes in the positive trials were broadly consistent with the primary results. In CLARITY AD the Alzheimer's Disease Assessment Scale-Cognitive Subscale and a daily-living scale for mild cognitive impairment favoured lecanemab, and CSF and plasma markers shifted toward a less pathological profile, with lower tau species and higher Aβ42 [27]. TRAILBLAZER-ALZ 2 similarly reported benefit on several clinical scales together with

substantial plaque clearance on PET [24]. Agreement between clinical and biomarker findings strengthens the interpretation that treatment is biologically active. It does not prove that biomarker change causes the clinical effect, and plasma markers in particular are still being validated as indicators of treatment response rather than only of diagnosis [17, 18].

Whether these effects matter to patients is the central interpretive question. A difference of 0.45 points on an 18-point scale is small in absolute terms, and estimates of the minimally important change on the CDR-SB from other work are larger, in the region of one to two points [34]. Supporters reply that a relative slowing of a quarter to a third, if it continued, would translate into months of preserved function over a longer period, and that average effects hide larger benefits in some individuals. Both views are defensible. What the trials cannot yet show is whether the treatment curves keep diverging beyond 18 months, since placebo-controlled follow-up ends there and open-label extensions lack a control group [7, 24, 27].

Systematic reviews generally reach cautious conclusions. A meta-analysis of published and unpublished trials found that antibodies reduced amyloid and had modest effects on cognitive measures, with a clear increase in ARIA [32]. A later review focusing on whether the benefits and harms were clinically important concluded that, on average, the benefits were small and below usual thresholds while the harms were meaningful [33]. These conclusions are sensitive to the choice of outcome and threshold, and they pool agents of very different potency, so they should be read alongside the individual trials. They do, however, serve as a counterweight to the more enthusiastic summaries of the main trials [32, 33].

5. SAFETY SIGNALS

Amyloid-related imaging abnormalities are the characteristic adverse effect of the class. They appear on MRI as ARIA-E, meaning parenchymal oedema or sulcal effusion, and ARIA-H, meaning microhaemorrhage and superficial siderosis, and they were first

formally described in a consensus paper written after the bapineuzumab experience [28]. The proposed mechanism involves antibody binding to amyloid in the walls of cerebral vessels, cerebral amyloid angiopathy, which is common in Alzheimer's disease; clearance of vascular amyloid is thought to compromise vessel wall integrity and raise permeability, leading to fluid leakage and bleeding [29, 35]. This explains why the risk is concentrated in people with more vascular amyloid.

Rates differ by agent and dose. With bapineuzumab the incidence of ARIA-E rose with dose and was highest in APOE $\epsilon 4$ carriers [19]. With high-dose aducanumab, ARIA-E occurred in roughly a third of participants in the phase 3 trials [36]. In CLARITY AD, ARIA-E occurred in about one in eight lecanemab recipients and ARIA-H in a larger share, and in TRAILBLAZER-ALZ 2 ARIA-E occurred in about a quarter of those given donanemab [24, 27]. Comparison between trials is limited by differences in MRI schedule, titration and population, and the lecanemab phase 2 study and its extension had previously suggested that ARIA clusters in the early months of treatment [25].

Other factors besides genotype modify the risk. Baseline microhaemorrhages and superficial siderosis, which indicate more advanced vascular amyloid disease, predict a higher chance of serious haemorrhage, and trials excluded patients with more than a few such lesions [28, 35]. Concomitant antithrombotic therapy is a second concern. Antiplatelet drugs at usual doses were allowed in the main trials, whereas anticoagulants were largely excluded, so evidence for safety in people taking them is thin [27, 30]. Radiologists and clinicians are therefore advised to treat a pre-treatment MRI as a risk assessment, not merely a baseline, and to document the number and location of microbleeds in the report [29, 37].

Genotype matters greatly. People who carry two copies of APOE $\epsilon 4$ have by far the highest risk, with about a third developing ARIA-E on lecanemab in the main study, compared with a much smaller fraction in non-carriers [27, 30]. Because the same

genotype also confers the highest risk of Alzheimer's disease, the group with the most to gain from treatment is also the group with the most to lose. For this reason, appropriate use recommendations advise testing for APOE genotype before treatment and discussing the results with the patient, and some experts regard homozygotes as a group in whom treatment should generally be avoided or approached with particular caution [9, 30, 31].

Most ARIA is asymptomatic and found only at scheduled MRI. When symptoms occur they include headache, confusion, dizziness, visual disturbance and, uncommonly, seizures or focal deficits, and the great majority of events resolve radiologically over weeks to months [25, 28]. Management follows MRI severity: mild events may allow continued dosing with closer imaging, whereas moderate or severe events lead to suspension of treatment until resolution [30, 37]. Rare severe haemorrhages and deaths have been reported, particularly when patients were given thrombolytics or were on anticoagulants, which is why clinicians are advised to take extra care with these medicines and to consider the possibility of ARIA in anyone treated who presents with acute neurological symptoms [30, 38].

Other adverse effects are less dramatic but frequent. Infusion-related reactions, mostly mild to moderate and presenting as fever, chills or flu-like symptoms, occurred in roughly a quarter of lecanemab recipients in CLARITY AD and were commonest at the first infusion [27]. Headache, falls and, with donanemab, a notable rate of infusion reactions, including some serious hypersensitivity events, were reported [24, 27]. Anti-drug antibodies develop in some patients, although their clinical relevance has not been clearly shown. Longer-term effects, including the significance of greater brain volume loss that has been observed with amyloid removal in several programmes, are not understood, and long-term surveillance and registries will be needed to settle them [33, 38].

Practical monitoring is demanding. Guidance recommends a baseline MRI before the first dose and further scans at set points in early

treatment, for example before the fifth, seventh and fourteenth infusions of lecanemab, with extra imaging whenever symptoms appear. Radiology departments must be able to recognise subtle oedema and microhaemorrhages, using standardised ARIA severity scales, and to report in a consistent way. Protocols that specify who orders scans, who reviews them, and how patients are contacted if a result changes the plan make the system safer, and they are best set up before the first patient is treated rather than after an incident [28, 30, 37].

6. IMPLICATIONS FOR PRACTICE

Appropriate use recommendations for lecanemab and aducanumab translate the trial criteria into clinical guidance. Candidates should have mild cognitive impairment or mild dementia of Alzheimer's type, a documented amyloid-positive biomarker, and a baseline MRI without extensive vascular disease, with exclusions that include multiple microhaemorrhages, superficial siderosis, a recent stroke and the use of anticoagulants [30, 31]. The guidance also emphasises APOE testing, counselling about the likelihood of ARIA, and a plan for follow-up. These criteria exclude a considerable fraction of memory clinic patients, and the proportion of patients actually eligible in routine care is likely to be well below the proportion who would like treatment [8, 16].

Delivery is a service-level challenge as well as a clinical one. Lecanemab is given by infusion every two weeks and donanemab every four, patients need amyloid confirmation, MRI before and during treatment, and clinicians with experience of dementia assessment and ARIA, and the whole pathway must be funded [8, 39]. Many health systems lack the PET and MRI capacity and the neurology workforce for substantial uptake. Costs of the drugs and of monitoring are high, and cost-effectiveness analyses are sensitive to assumptions about whether effects persist after 18 months. Equity concerns arise if access depends on geography and insurance. For these reasons, pathway design and prioritisation are as important as the decision about whether a drug should be approved [7, 33].

Decisions about stopping are as important as those about starting. In the donanemab programme, dosing was discontinued once amyloid fell below a preset PET threshold, while lecanemab was continued for the whole trial period [24, 27]. Outside trials, clinicians must decide when to stop because of ARIA, disease progression to a stage beyond that studied, intolerance or patient preference, and the appropriate use recommendations suggest regular reassessment with cognitive testing and consideration of stopping when the patient moves beyond mild dementia [30, 31]. Evidence on what happens after treatment is withdrawn is scarce. Whether amyloid reaccumulates and decline then speeds up is a question that long-term follow-up of treated cohorts should address [8].

Counselling requires honesty about what the drugs do. The trials show slowing of decline over 18 months by roughly a quarter to a third on the main scale, with no improvement of symptoms and no halting of disease [24, 27]. Patients and families who expect recovery will be disappointed, and those who expect nothing may not understand why neurologists consider the findings important. Shared decision making should cover the monitoring burden, the chance of ARIA and its genotype dependence, the uncertainty around long-term benefit and the possibility of stopping. The spread of the evidence by type is shown in fig. 1; it is weighted toward trial results and thinner on safety management and evidence synthesis [32, 33, 34].

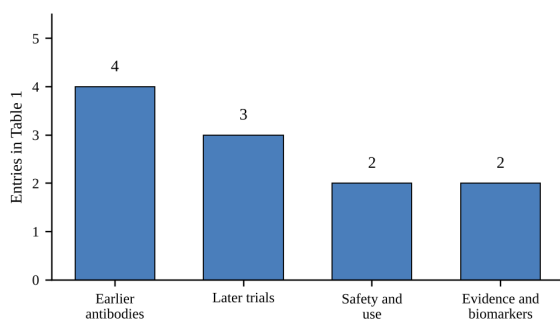


Fig. 1: Number of entries in table 1 by category

Pharmacists and nurses have a natural part in these pathways. Medication review before treatment can identify anticoagulants, antiplatelet combinations and other drugs that raise bleeding risk, and counselling on infusion reactions and warning symptoms is a task that suits clinical pharmacy teams.

Dosing schedules, premedication practice and handling of the infusion product are further points that fall within pharmacy responsibility. Written information for patients and carers should explain which symptoms need urgent contact, such as new severe headache, confusion or visual change, so that ARIA is not missed outside scheduled MRI visits [8, 30].

7. LIMITATIONS AND FUTURE DIRECTIONS

Trial design and outcome measurement also affect what can be concluded. The CDR-SB combines caregiver and clinician judgement across six domains and is sensitive in early disease but coarse, and the integrated rating scales used in some trials are composites whose clinical meaning is less intuitive [24, 27, 34]. Eighteen months is short against a disease that evolves over a decade, and drop-out and ARIA-related unblinding, since MRI findings may reveal treatment allocation, could bias subjective ratings. Methodologists have asked for outcome measures anchored in patient and carer-reported function and for transparent handling of these risks of bias [7, 33].

Amyloid removal addresses only one part of the disease. Tau pathology correlates more closely with cognitive impairment than amyloid does, and tau burden predicts who responds less well, a finding that is built into the design of the donanemab phase 3 trial [24, 40]. This leaves open the question of whether combining anti-amyloid and anti-tau approaches, or adding treatments that target inflammation, vascular risk or synaptic function, would give larger benefits. The drug development pipeline is wide, with many agents directed to targets other than amyloid, but few have yet shown clinical efficacy [39]. The anti-amyloid antibodies, in other words, may be a first step and not a complete answer.

Intervening earlier is a logical extension. Prevention trials in people who are cognitively unimpaired but amyloid positive, such as the AHEAD 3-45 study, test whether removing amyloid before symptoms emerge can delay or avoid decline [41]. If successful, such strategies would need accurate and scalable screening, and plasma p-tau217 and

related blood tests are the leading candidates [17, 18]. Other practical goals include antibodies engineered to cross the blood-brain barrier more efficiently, which might lower the dose required and the risk of ARIA, and subcutaneous formulations that avoid infusion visits, though these remain under investigation [8, 39].

Evidence gaps remain even for the approved drugs. There are no head-to-head trials, so statements about relative efficacy are indirect. Follow-up beyond 18 months of controlled data is lacking, and the populations studied were not representative of the full range of patients. Full individual participant data, which would allow independent analysis of subgroups and of the link between amyloid reduction and clinical change, have not been widely shared [7, 33]. Real-world registries will help, provided they capture ARIA outcomes, cognition, function and caregiver burden in a standard way, and provided results are reported openly whatever they show [32, 34].

Ethical and communication issues deserve a place in the research agenda. Biomarker-based diagnosis can now identify people at risk years before symptoms, and decisions about disclosure, insurance and employment follow from that. Public messaging about new drugs has sometimes outrun the data, with headlines suggesting a cure when the trials showed slowing. Researchers can contribute by using clear language in publications, reporting absolute as well as relative differences and giving ARIA data in a form that clinicians can use. Patient and carer groups are increasingly involved in setting priorities, and their view of what counts as a meaningful benefit may differ from that of trial statisticians [7, 33, 34].

8. CONCLUSION

Anti-amyloid antibodies have moved the amyloid hypothesis from a long record of disappointment to partial vindication. Lecanemab and donanemab, given to biomarker-confirmed patients with early disease, slow clinical decline over 18 months by about a quarter to a third on the main scales, while earlier and weaker antibodies

did not, and the contrast points to potency of amyloid clearance, patient selection and timing as the main variables [15, 20, 24, 27]. The benefit is real but modest in absolute terms and its long-term durability is unknown [33, 34]. Taking the trial programme as a whole, the field has learned that a hypothesis can be right in outline and still need years of refinement before it helps anyone [3, 23].

These gains come with ARIA, rare but serious bleeding, infusion reactions and a heavy monitoring burden, and the risk is greatest in APOE ϵ 4 homozygotes [28, 29, 30]. Responsible use means careful selection, genotype counselling, scheduled MRI and clear communication of expected benefit [30, 31]. Future progress will probably depend on earlier treatment, blood-based screening, safer delivery and combinations that address tau and other pathways, with open reporting of long-term outcomes [17, 39, 41]. Until then, these antibodies are best seen as a first, imperfect step that works for a defined minority of patients and demands strong health-service support [8, 40].

9. ABBREVIATIONS

A β -Amyloid-beta, AD-Alzheimer's disease, APOE-Apolipoprotein E, ARIA-Amyloid-related imaging abnormalities, ARIA-E-ARIA with oedema or effusion, ARIA-H-ARIA with haemosiderin deposition, CDR-SB-Clinical Dementia Rating Sum of Boxes, CSF-Cerebrospinal fluid, MRI-Magnetic resonance imaging, PET-Positron emission tomography, p-tau217-Phosphorylated tau at threonine 217

10. FUNDING

Nil

11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

1. Hardy J, Higgins G. Alzheimer's disease: the amyloid cascade hypothesis. *Science* 1992;256:184–5.
2. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med* 2016;8:595–608.

3. Karran E, De Strooper B. The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics. *Nat Rev Drug Discov* 2022;21:306–18.
4. Jack CR Jr, Bennett DA, Blennow K, *et al.* NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018;14:535–62.
5. Albert MS, DeKosky ST, Dickson D, *et al.* The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:270–9.
6. Jack CR Jr, Andrews JS, Beach TG, *et al.* Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement* 2024;20:5143–69.
7. Liu KY, Howard R. Can we learn lessons from the FDA's approval of aducanumab? *Nat Rev Neurol* 2021;17:715–22.
8. Cummings J, Osse AML, Cammann D, Powell J, Chen J. Anti-amyloid monoclonal antibodies for the treatment of Alzheimer's disease. *BioDrugs* 2024;38:5–22.
9. Corder EH, Saunders AM, Strittmatter WJ, *et al.* Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921–3.
10. Walsh DM, Selkoe DJ. A β oligomers: a decade of discovery. *J Neurochem* 2007;101:1172–84.
11. Sevigny J, Chiao P, Bussière T, *et al.* The antibody aducanumab reduces A β plaques in Alzheimer's disease. *Nature* 2016;537:50–6.
12. Swanson CJ, Zhang Y, Dhadda S, *et al.* A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-A β protofibril antibody. *Alzheimers Res Ther* 2021;13:80.
13. Mintun MA, Lo AC, Duggan Evans C, *et al.* Donanemab in early Alzheimer's disease. *N Engl J Med* 2021;384:1691–704.
14. Söderberg L, Johannesson M, Nygren P, *et al.* Lecanemab, aducanumab, and gantenerumab: binding profiles to different forms of amyloid-beta might explain efficacy and side effects. *Neurotherapeutics* 2023;20:195–206.
15. Bateman RJ, Smith J, Donohue MC, *et al.* Two phase 3 trials of gantenerumab in early Alzheimer's disease. *N Engl J Med* 2023;389:1862–76.
16. Rabinovici GD, Gatsonis C, Apgar C, *et al.* Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia. *JAMA* 2019;321:1286–94.
17. Hansson O, Blennow K, Zetterberg H, Dage J. Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nat Aging* 2023;3:506–19.
18. Palmqvist S, Janelidze S, Quiroz YT, *et al.* Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA* 2020;324:772–81.
19. Salloway S, Sperling R, Fox NC, *et al.* Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med* 2014;370:322–33.
20. Doody RS, Thomas RG, Farlow M, *et al.* Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med* 2014;370:311–21.
21. Honig LS, Vellas B, Woodward M, *et al.* Trial of solanezumab for mild dementia due to Alzheimer's disease. *N Engl J Med* 2018;378:321–30.
22. Ostrowitzki S, Bittner T, Sink KM, *et al.* Evaluating the safety and efficacy of crenezumab vs placebo in adults with early Alzheimer disease: two phase 3 randomized placebo-controlled trials. *JAMA Neurol* 2022;79:1113–21.
23. Haass C, Selkoe D. If amyloid drives Alzheimer disease, why have anti-amyloid therapies not yet slowed cognitive decline? *PLoS Biol* 2022;20:e3001694.
24. Sims JR, Zimmer JA, Evans CD, *et al.* Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA* 2023;330:512–27.
25. Honig LS, Barakos J, Dhadda S, *et al.* ARIA in patients treated with lecanemab (BAN2401) in a phase 2 study and open-label extension. *Alzheimers Dement (N Y)* 2023;9:e12377.
26. Budd Haeberlein S, Aisen PS, Barkhof F, *et al.* Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *J Prev Alzheimers Dis* 2022;9:197–210.
27. van Dyck CH, Swanson CJ, Aisen P, *et al.* Lecanemab in early Alzheimer's disease. *N Engl J Med* 2023;388:9–21.

28. Sperling RA, Jack CR Jr, Black SE, *et al.* Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement* 2011;7:367–85.
29. Hampel H, Elhage A, Cho M, Apostolova LG, Nicoll JAR, Atri A. Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics. *Brain* 2023;146:4414–24.
30. Cummings J, Apostolova L, Rabinovici GD, *et al.* Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis* 2023;10:362–77.
31. Cummings J, Aisen P, Apostolova LG, *et al.* Aducanumab: appropriate use recommendations. *J Prev Alzheimers Dis* 2021;8:398–410.
32. Lacorte E, Ancidoni A, Zaccaria V, *et al.* Safety and efficacy of monoclonal antibodies for Alzheimer's disease: a systematic review and meta-analysis of published and unpublished clinical trials. *J Alzheimers Dis* 2022;87:101–29.
33. Ebell MH, Barry HC, Baduni K, Grasso G. Clinically important benefits and harms of monoclonal antibodies targeting amyloid for the treatment of Alzheimer disease: a systematic review and meta-analysis. *Ann Fam Med* 2024;22:50–62.
34. Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement (N Y)* 2019;5:354–63.
35. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease: one peptide, two pathways. *Nat Rev Neurol* 2020;16:30–42.
36. Salloway S, Chalkias S, Barkhof F, *et al.* Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. *JAMA Neurol* 2022;79:13–21.
37. Barakos J, Purcell D, Suhy J, *et al.* Detection and management of amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with anti-amyloid beta therapy. *J Prev Alzheimers Dis* 2022;9:211–20.
38. Withington CG, Turner RS. Amyloid-related imaging abnormalities with anti-amyloid antibodies for the treatment of dementia due to Alzheimer's disease. *Front Neurol* 2022;13:862369.
39. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2024. *Alzheimers Dement (N Y)* 2024;10:e12465.
40. Bejanin A, Schonhaut DR, La Joie R, *et al.* Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. *Brain* 2017;140:3286–300.
41. Rafii MS, Sperling RA, Donohue MC, *et al.* The AHEAD 3-45 Study: design of a prevention trial for Alzheimer's disease. *Alzheimers Dement* 2023;19:1227–33.