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REVIEW ARTICLE

A Narrative Review on Preclinical/Clinical Trials on Aducanumab

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Abstract

The most widespread type of dementia, Alzheimer's disease (AD), is predicted to triple in global prevalence by 2050. AD has a substantial societal and economic impact across the world, negatively affecting both patients and their caregivers, as the disorder has few therapeutic alternatives. Aducanumab was the first monoclonal antibody approved in 2021 for the treatment of mild AD. Representing the first AD drug approval in 20 years and based on the concept of targeting amyloid-β (Aβ) as an immunisation treatment for AD, aducanumab was demonstrated to reduce Aβ plaque formation in animal models and humans. This was used as a proxy of efficacy in AD clinical trials to slow disease progression and reduce cognitive decline in AD. Culminating from the Aβ hypothesis of AD that has dominated the focus of AD drug development since its inception, aducanumab, for many, represents validation of the hypothesis and promise for the future. This review examines the antibody research, preclinical and clinical studies, that underpin the development of aducanumab as an AD medication. No single drug is generally likely to cure a complex, progressive and heterogeneous degenerative disorder, but it may act as a stepping stone towards greater understanding and potentially more effective treatment options. Time will ultimately tell in the case of aducanumab as to whether it is a small or large step in the correct or incorrect direction to unravel the mystery of this complex disorder and provide a worthwhile treatment.

Key words: Aducanumab; Alzheimer's disease; Amyloid beta-peptides; Anti-dementia agents; Dementia; Antibodies, monoclonal.

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Introduction

Alzheimer's disease (AD) is a common neurodegenerative disease that results in progressive cognitive impairment. This chronic condition affects approximately 55 million people worldwide and has a substantial negative impact on quality of life, productivity and the economy.[1] AD accounts for over 60–80 % of all dementia cases.[2] Although the causes of AD are undoubtedly multiple and remain largely unknown, the disease is highly age-dependent and associated with environmental and genetic factors, together with lifestyle choices. The development of AD is characterised by the presence of Aβ protein peptide aggregates and neurofibrillary tangles in key brain regions, which impair neuronal function and ultimately cause neuronal demise.[3] Additional prominent factors include synaptic loss, inflammation (brain and systemic), cerebrovascular amyloidosis and

decreased neurotransmitter concentrations.[4] Despite breakthroughs in AD imaging, neurobiology and genetics, these have largely not translated into drug investigation and development success and thus, a cure for the disease remains elusive.

The majority of approved AD medications were designed to treat the disorder symptoms rather than the potential underlying cause of the disease.[5] Cholinesterase inhibitors (donepezil, rivastigmine and galantamine), as well as potentially neuroprotective N-methyl-D-aspartate receptor antagonists (memantine), are commonly used to treat the symptoms of AD.[6, 7] A variety of therapeutics to potentially modify the biology of AD have been preclinically developed and multiple have been evaluated in clinical trials. The vast majority of these have attempted to leverage knowledge derived from AD genetic and neurobiology discoveries and target Aβ in some manner, either as monoclonal antibodies to bind and clear different species within the Aβ aggregation cascade or to reduce the processing/metabolism of amyloid precursor protein into generating Aβ. Such treatment approaches are grounded on the "amyloid hypothesis," which posits that Aβ aggregates initiate a torrent of events, comprising synaptic impairment, network dysfunction, neuroinflammation and the seeding and spread of hyperphosphorylated phospho-tau neurofibrillary tangles (p-tau NFTs). NFTs' outspread is accompanied by synaptic loss and neurodegeneration, ultimately leading to cognitive decline and dementia. By binding and clearing Aβ aggregates using a monoclonal approach, or reducing Aβ generation by a secretase inhibitor approach, Aβ targeted medications can theoretically both the direct as well as downstream adverse actions of Aβ to potentially slow cognitive decline – unless such downstream effects are self-propagating once they have been initiated. This hypothesis largely accounts for the two histopathological features of AD: the existence of beta amyloid plaques surrounded by activated microglia cells and the presence of NFTs chiefly composed of hyperphosphorylated Tau protein. However, there are many examples of individuals with abundant amyloid deposits in the brain and no signs of AD, as well as examples of patients with AD possessing minimal Aβ deposition. Nevertheless, the genetic evidence for a causal role of Aβ in AD is overwhelming.

Aducanumab was first generated by Neuroimmune and the license was later sold to Biogen in 2007.[8] On 7 June 2021, the Food and Drug Administration (FDA) gave aducanumab expedited approval as the first disease-modifying drug for the treatment of AD. This monoclonal antibody recognises soluble Aβ oligomers and insoluble aggregates of Aβ proteins.[9]

The current article reviews the history of aducanumab, antibody research in AD therapies and preclinical and clinical studies.

Generation of aducanumab: targeting Aß as a therapeutic modality

Numerous structural, functional and neuropathological mechanisms potentially involved in the development of AD have been identified. Of these, the amyloid cascade is one of the more persistent theories addressing the pathophysiology of AD and has captured and retained the interest of academics and medication developers for years. Hardy and Higgins planted the seed leading to the amyloid theory in 1992.[10] According to this theory, an aberrant build-up of Aβ plaques in the brain cortex is the originating cause of neurodegeneration in AD.[11]

Aβ peptides having 39–42 amino acid residues, which are produced by the proteolysis of the amyloid-β protein precursor (APP) by the cleaving enzyme actions of β-secretase and γ-secretase are key elements of amyloid plaques. The Aβ1-42 isoform deposits more rapidly, aggregates more quickly and forms a fundamental component of all such plaques. Among the induction of multiple secondary and tertiary events, an inflammatory response and the molecular cascade of microglial activation result from this Aβ deposition and plaque development.[12]

Under normal conditions during healthy aging, the enzyme activity of α-secretase predominantly cleaves APP within the amyloid-β domain so that insoluble forms of Aβ, which ultimately cause amyloid build-up are not generated[13] and the small physiological amounts that are generated can be effectively cleared by homeostatic mechanisms. Following excessive Aβ generation and oligomerisation, the aberrant phosphoryla-

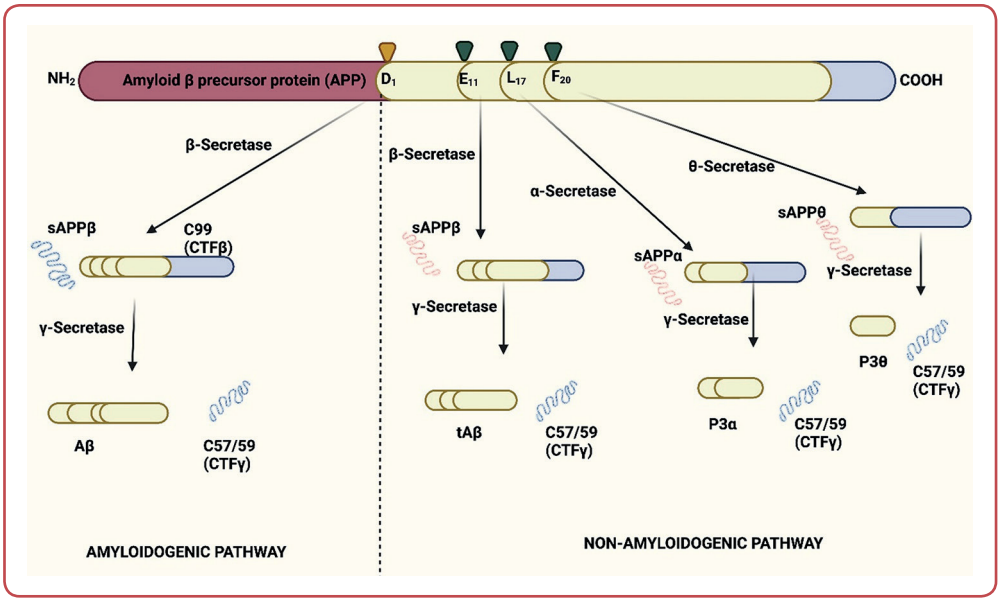

Figure 1: In the processing of amyloid precursor protein (APP), two main pathways exist: amyloidogenic and non-amyloidogenic. In the amyloidogenic pathway, APP is initially cleaved by the enzyme Beta-secretase 1 (BACE1) at the aspartic proteinase 1 (Asp1) site, resulting in the release of a soluble amyloid precursor protein released by a-secretase (sAPPβ) and leaving a membrane-bound 99-amino acid (A.A) C-terminal fragment known as C99. This fragment is further cleaved by γ-secretase, releasing amyloid-β (Aβ) peptides and a smaller C-terminal fragment (CTF)

tion of microfibrillar tau-proteins can occur and is known to both seed and increase the amount of hyperphosphorylated tau, a further key feature in the pathogenesis of AD.[14] The final developmental pathways for AD are alterations in endocytosis, cholesterol metabolism, immune/inflammatory processes, amyloid-β metabolism and angiogenesis.[15] Multiple AD-related changes in a host of proteins have been identified over past decades and amongst these, predictive alterations in cortical amyloid positron emission tomography (PET)-binding and a decreased Aβ42/Aβ40 ratio in the cerebrospinal fluid (CSF) are two examples that have become useful biomarkers for AD.[16] Amyloid cascade is represented in Figure 1.

In contrast, the non-amyloidogenic pathway prevents Aβ production under normal physiological conditions. Here, α-secretase cleaves APP within the Aβ domain at the leucine[17] site, producing a secreted form of APP, soluble amyloid precursor protein released by a-secretase (sAPPα) and an 83-amino acid C-terminal fragment, C83. BACE1 can also process APP at the Glu11 site, yielding C89, which is subsequently cleaved by γ-secretase to produce a shortened Aβ peptide, Aβ11-40. Additionally, BACE2 cleaves APP at the Phe20 site, generating C80 and blocking Aβ formation altogether.

History of AD and failures of different attempts targeting

Scientists first found that AD is caused by the deposition of sticky plaques, Aβ and in the 1990s, they found that this Aβ was responsible for the neuronal damage that causes memory loss and AD. This is known as the amyloid hypothesis. The idea of removing these sticky plaques from the brain then comes out, first thought is to treat with the help of a vaccine, which would train the immune system to find and hunt down Aβ and would treat AD. First, a company called Elan made a vaccine and tested it on 400 patients, but the trial failed due to serious side effects such as brain inflammation in 6 % of patients. Thus, it was concluded that the vaccine might not be safe and the idea of injecting synthetic antibodies was developed. In 2006, *Lilly* made solanezumab and *Pfizer* crafted bapineuzumab. In 2011, these companies tested these two antibodies and failed. In 2016, *Biogen* developed aducanumab and tested it, but again failed. All these failures cause long-time critics of the amyloid hypothesis.[17-19]

Current anti-amyloid treatments for AD target Aβ in three main ways: inhibiting its production, enhancing its clearance and preventing its aggregation into plaques. These approaches

are influenced by factors such as the amount, rate, location, reversibility and duration of Aβ deposition in the brain.[20-22] Monoclonal antibodies, designed to target Aβ specifically, have been central to immunotherapeutic strategies, primarily through passive immunotherapy. Despite extensive research and some successes, these treatments have faced challenges, including toxicity issues that have led to the halting or modification of some studies.[23, 24]

There have been numerous attempts to produce drugs that target Aβ without much success.[25, 26] The monoclonal antibodies that target amyloid and tau in AD are compiled along with their current clinical status by Mukhopadhyay et al.[27]

In 2019, Selkoe et al revealed the Biogen's phase-I trial results and possible causes of these disappointing results of aducanumab.[28] The unsatisfactory results of these recent trials have four possible causes. First, it is inaccurate to assume that the years-long plaques of Aβ are the beginning of the disease's symptoms. It means that the "amyloid hypothesis," on which Scientists have been working for more than 30 years, is unproven. Second, the majority of patients in the aducanumab trial might have been too symptomatic, too far along in the biology of the illness for the process to be considerably slowed, at least when seen as a whole. Third, numerous investigations have revealed that the major type of amyloid-soluble Aβ oligomers, which may be synaptotoxic and microglia-stimulating are not properly neutralised and cleared by aducanumab. Fourth, Combination therapy is the only way to treat AD and modify the condition.

The available medications for AD might provide some temporary relief from its cognitive symptoms, but they are not necessarily going to treat the disease. So, there has been a lot of active research for new and improved medications. Aducanumab, 'an amyloid plaque removal' and a monoclonal antibody administered intravenously (IV). Some promising results were shown in the year 2016, that in the mild cognitive impairment (MCI)/mild cases, amyloid was cleared from the brain. On the other hand, they were also shown some safety concerns at higher doses, eg Amyloid-related imaging abnormality (ARIA) microbleeds, but the results were promising enough to study further. So, the Phase 1b trial was conducted and then Phase 2. After that, the phase 3 trial was launched, ie EMERGE and ENGAGE. But in 2019, *Biogen* (the company that is producing aducanumab) ended the trial due to lack of efficacy, so they decided not to take the risk; it seemed it might be the end of the story.

But then *Biogen* continued to analyse some other data and found that in one particular trial, ie EMERGE and one subgroup, the people receiving the higher dose showed less decline over time than the placebo-controlled group. So, based on this finding, *Biogen* again starts a study.

In January 2020, the FDA allowed *Biogen* to proceed with the study again and relaunched this study to go back to their participants, but in November 2020, the FDA didn't find impressive results, so the advisory committee didn't approve the medication; they asked for continuous results from the company. In June 2021, the FDA approved the drug after satisfactory data from *Biogen*. A timeline of the tale of the drug and events is explained in Figure 2.

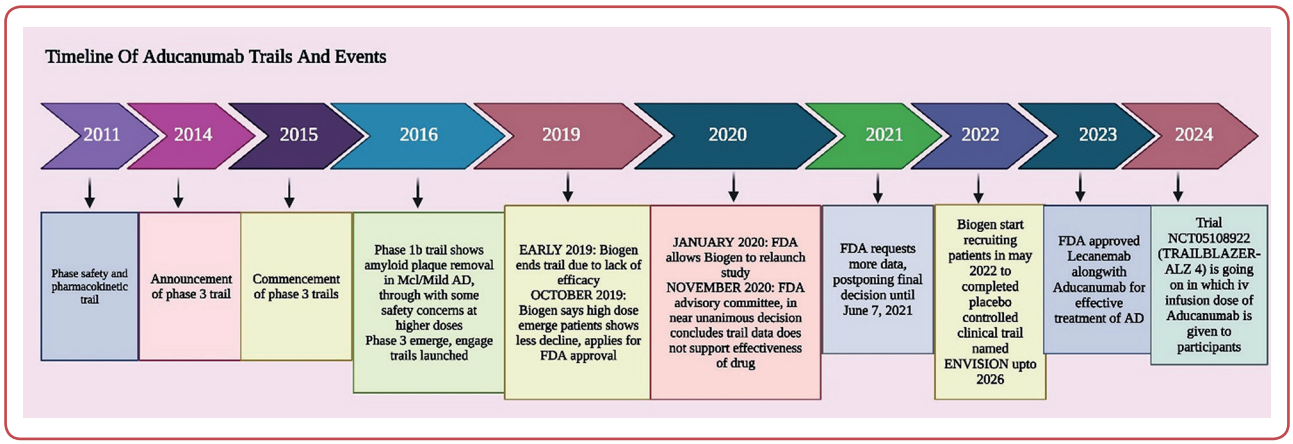

Figure 2: Timeline of aducanumab's trials and events

Antibody research in AD

Numerous antibody therapeutics targeting Aβ, including bapineuzumab, solanezumab, ganterenumab and crenezumab, have been developed preclinically and translated into clinical evaluation.[29] Unfortunately, the Dominantly Inherited Alzheimer Network Trial Unit (DIAN-TU) and Alzheimer's Disease Neuroimaging Initiative (ADNI) trials with these medications have largely failed to provide any clinically significant results over time. Although significantly lowering cerebrospinal fluid (CSF) p-tau, bapineuzumab did not outperform a placebo concerning cognitive outcomes and was associated with more severe side effects.[30] In two phase 3 trials, crenezumab failed to accomplish the primary endpoint. Furthermore, ARIA was noted as an unexpected side effect. In a dementia prevention experiment with ganterenumab and solanezumab, derived from DIAN-TU research, ganterenumab exhibited a significant impact on select markers of biomarker burden but displayed no effect on cognitive symptoms. Solanezumab, in contrast, failed to demonstrate improvement in any area. Whereas those who were asymptomatic did not appear to become worse, those who were symptomatic continued to lose cognitive function before receiving the intended dose. Another amyloid plaque targeting antibody, donanemab, was found to yield contradictory results on the primary and secondary cognitive rating scales.[31, 32] The clinical evidences is shown in Table 1.

Table 1: Clinical evidence of antibodies' effects on Alzheimer's disease (AD) hallmarks. The table shows the origin and different epitopes of amyloid-β (Aβ) recognised from the different tested substance and their efficacy

Substance	Origin	Aβ epitope	Effects	Phase	Clinical trial identifier	Administration and participants	Ref.
Aducanumab	Human Immunoglobulin G (IgG)1	A.A. 3-7	Decrease in Aβ Decrease p-Tau in Cerebrospinal fluid (CSF) and positron emission tomography (PET)	Approved	National clinical trial (NCT) NCT02782975 NCT02477800	Intravenous prodomal to mild AD	[33,34]
Bapineuzumab	Humanised IgG1	A.A. 1-5	Reduction in fibrillar Aβ p-Tau decrease in CSF Correlation Aβ/Tau reduction in Apolipoprotein E (APOE) ε4	Discontinued in Phase 3	NCT03531710 NCT00575055 NCT00574132	Intravenous, mild to moderate AD	[35,36]
Gantenerumab	Humanised IgG1	A.A. 3-12, 18-27	Reduction in Aβ, Reduction p-Tau and t-Tau in CSF	II and III	NCT03443973	Subcutaneous, individual at risk	[37]
Donanemab	Humanised IgG1	N-terminal pyroglutamate Aβ	Reduction in Aβ plaques, Reduction in Tau accumulation in the frontal and temporal lobes	Approved	NCT01837641	Intravenous early/mild AD	[38]
AN-1792	Synthetic full-length Aβ peptide, QS-21 adjuvant	Aβ N-terminus	Aβ clearance by microglia p-Tau reduction	Discontinued	NCT00021723	Intramuscular mild to moderate AD	[39]

Aducanumab preclinical / clinical studies

During 2016, initial studies conducted by Kastanenka and colleagues, following treatment of AD mice, concluded that a murine analogue of aducanumab improved select functional outcome measures. It cleared amyloid plaques in an acute setting and, when administered chronically to elderly AD mice, reestablished brain calcium homeostasis that had become dysfunctional in AD mice without impacting amyloid plaque load. As dysregulation of intracellular calcium levels can result in functional abnormalities in neuronal networks that may underline memory deficits in humans, such positive effects in calcium imaging could potentially be used as a proxy for a functional outcome. This was interpreted as improving a functional outcome measure reflective of neural network activity. The inability of these elderly AD mice to remove their pre-existing amyloid plaques was considered compatible with the theory that immunotherapy may be beneficial for

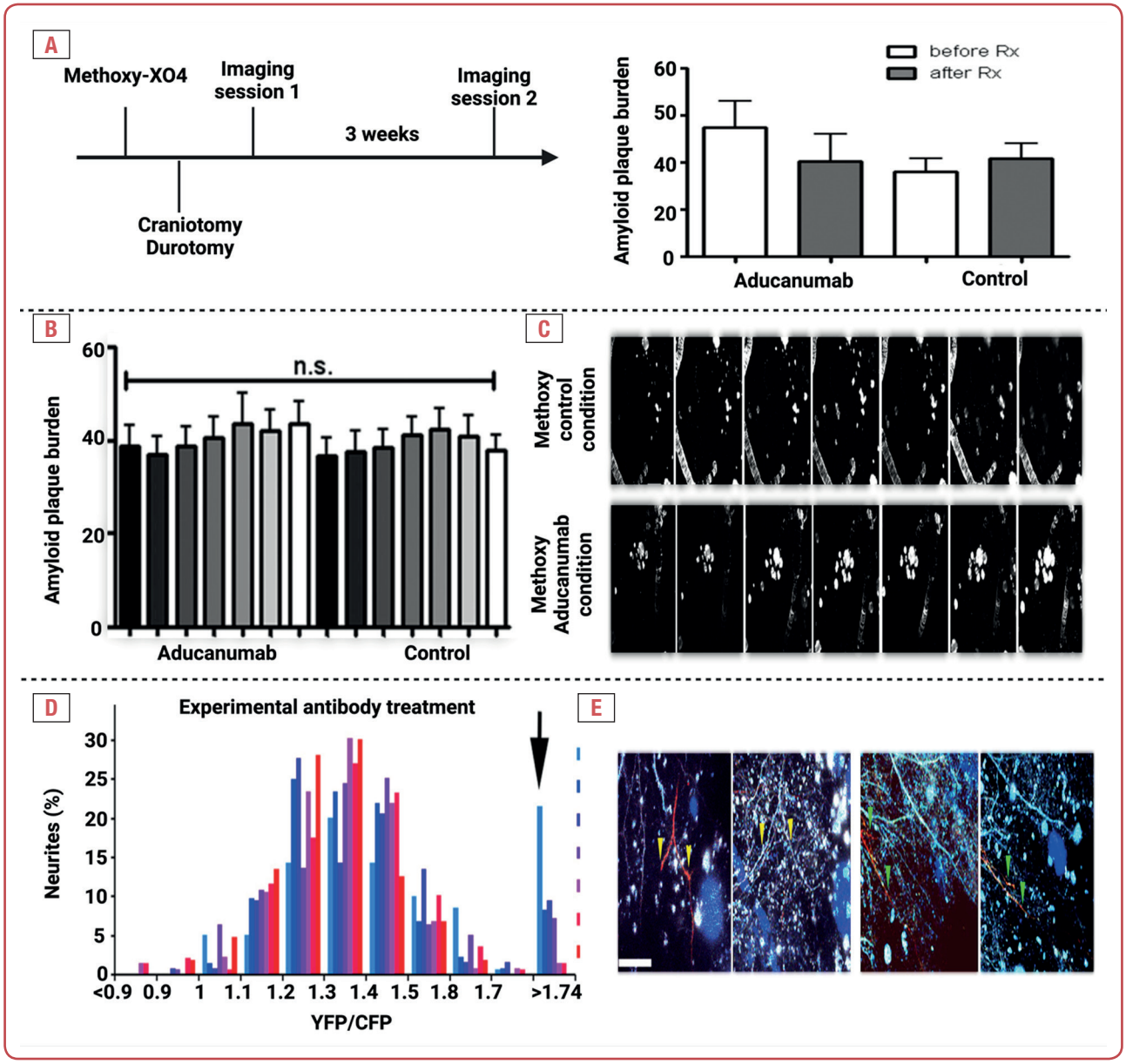

Figure 3: A: Figure showing aducanumab administration does not clear plaques in very old Tg2576mice. B: Amyloid burden as compared to the control antibody. C: Two-photon images of amyloid deposit and cerebral amyloid angiopathy (CAA) in the mouse cortex treated with control antibody. D: Neurite calcium burden is restored with aducanumab immunotherapy treatment. E: Red neurites indicate the presence of increased levels of calcium, whereas blue neurites display usual calcium levels. Reprinted from reference 40 under an open access license

treating amyloidosis in its early stages but less successful in advanced stages where significant parenchymal plaque deposits may already be present – but, at this stage, may nevertheless re-instate calcium homeostasis.[40]

Conceptually, behavioural tests in mice are attractive for the assessment of cognitive impairments because they provide a clear functional outcome. However, amyloid-β immunotherapy studies have had mixed outcomes, with effects on parenchymal Aβ frequently associated with little or very slight recovery of memory impairments.[40]

The results of the study are shown in Figure 3.

During the same year, Sevigny and colleagues[33] reported interim results from a double-blind, placebo-controlled phase 1b randomised trial evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of monthly aducanumab infusions in patients with prodromal or mild AD with brain Aβ pathology confirmed by PET imaging. They additionally reported results from AD mice studies within the same publication.[33] The results reported the selective binding of aducanumab to insoluble fibrillar and soluble

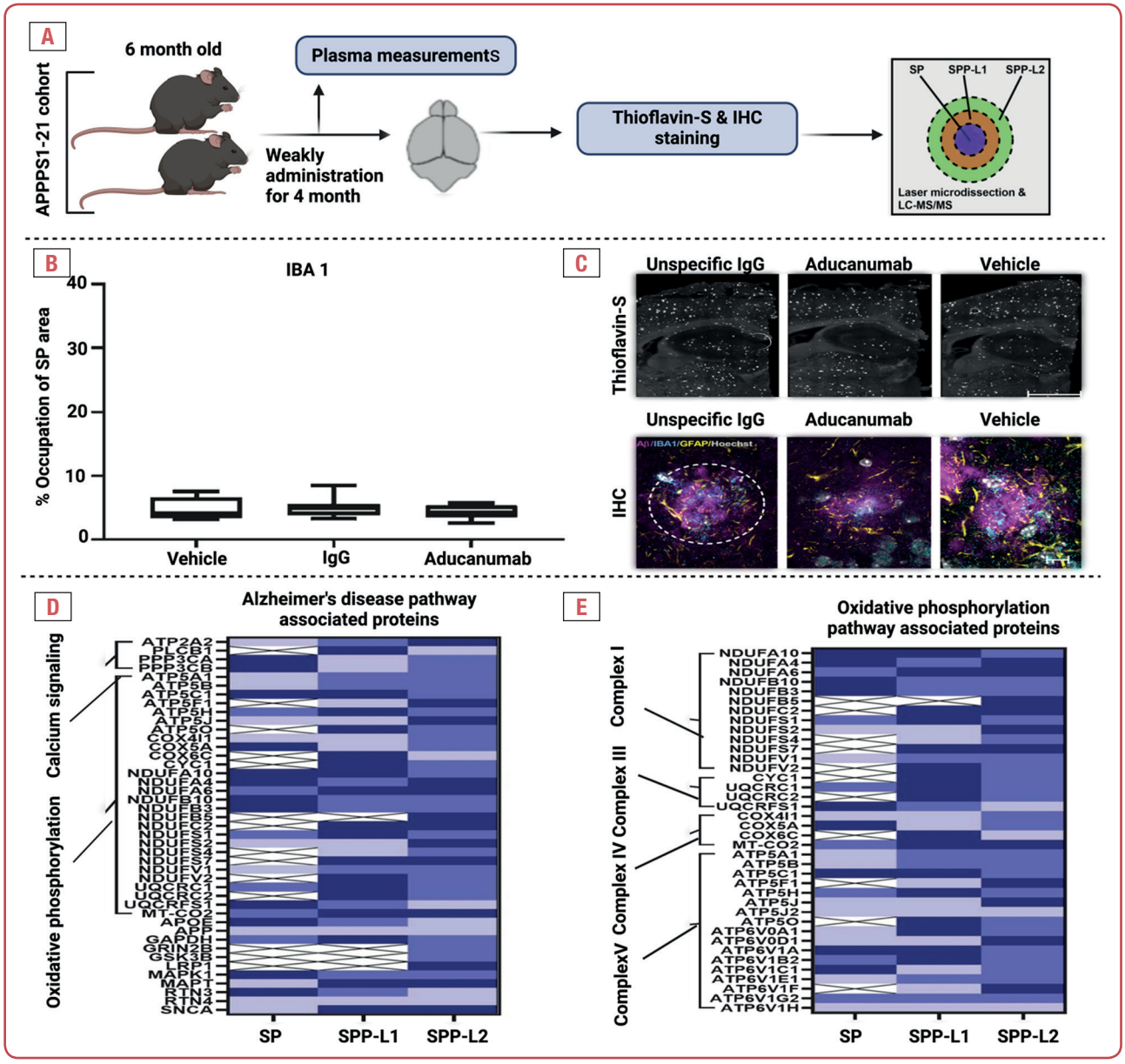

Figure 4: A: Experimental design of the study. B: Administration of aducanumab on IBA1-positive microglia (no changes in either microglia or astrocytes were evident). C: Thioflavin-S staining of brain sections [to identify senile (amyloid plaques). D and E: Pathway associations of identified proteins. Reprinted from reference 41 under an open access license

oligomeric Aβ aggregates, with low binding to monomeric soluble Aβ40. A dose-dependent reduction in amyloid burden in 9.5- to 15.5-month-old Tg2576 AD mice, with declines in both Aβ42 and Aβ40 and a brain/plasma drug ratio of 0.0059 [ie 0.59 %] measured at Cmax. An aducanumab dose- and time-dependent reduction in brain florbetapir PET imaged Aβ plaques in human AD subjects that were accompanied by dose-dependent improvements in select clinical measures, the Clinical Dementia Rating—Sum of Boxes (CDR-SB) scale and Mini-Mental State Examination, but not in a composite neuropsychological test battery. Positive actions were reported in both APOE4 carriers and non-carriers, although the patient numbers were relatively small. The authors favourably concluded that aducanumab may have positive effects on neural network function, which potentially underlies cognitive problems and should be evaluated in larger, more extensive AD human clinical studies as a possible AD treatment.

In evaluating potential mechanisms via which aducanumab treatment could potentially benefit AD subjects, Bastrup et al. In 2021,[41] performed a localised proteome study by merging laser microdissection and liquid chromatography-mass spectrometry (LC-MS/MS) methods to characterise three regions associated with amyloid plaques in AD mice following 4-month aducanumab vs control treatment. They identified an aducanumab-associated alteration in key proteins involved in [i] mitochondria and metabolism (upregulated), [ii] cytoskeleton and axons, [iii] stress response (downregulated) and [iv] APP trafficking and processing (downregulated). They interpreted this as aducanumab creating a beneficial proteomic microenvironment around amyloid plaques to potentially lessen Aβ toxicity and increase phagocytosis and cell viability. The primary outcomes of the study are shown in Figure 4 and whether such actions translate to human AD remains to be determined, but provide a potentially useful focus for future investigation(s).

In this light, with the advent of conformationally specific immunotherapy methods, the important amyloid species that potentially initiates and drives the neurodegenerative cascade could, in theory, be targeted without interacting with unrelated Aβ species that may have a physiological role, to hypothetically optimise efficacy and/or reduce adverse actions. Sevigny and colleagues[33] presented their florbetapir PET as mean standard uptake value ratio (SUVR) composite scores combined across 6 cortical brain regions.

In a later study, Chiao et al, with largely the same aim, successively evaluated the potential efficacy of aducanumab against AD in the PRIME phase 1b clinical study. They reported dose and time-dependent reductions in Aβ PET SUVRs only in cortical regions susceptible to amyloid plaque deposition; thereby supporting aducanumab's purported ability to remove Aβ.[34]

Subcortical white matter, cerebellar white matter and the pons provided the highest sensitivity of SUVRs for assessing longitudinal changes in Aβ in response to therapy in relation to the reference regions examined. Greater effect sizes were noted when the anterior cingulate cortex was used as the target ROI as opposed to the composite cortex.[34]

The findings of Arndt and colleagues offer a structural explanation for aducanumab's lower affinity for non-pathogenic monomers and higher selectivity for forms compared to previous Aβ targeting antibodies. In this regard, aducanumab is reported to bind to the N-terminus of Aβ differently from other antibodies that, likewise, target this immunodominant epitope, as depicted by the crystal structure of the Fab fragment of aducanumab on attachment to its epitope peptide. On the surface of the antibody, aducanumab detects a small epitope that is contained in a small pocket. Aducanumab's limited interactions with the Aβ monomer and its apparent ability to accommodate different peptide conformations, as suggested by *in silico* analyses, underpin the selectivity of the drug for Aβ aggregates.[42]

Comparision of aducanumab alongside other therapeutic candidates, indicating that while it effectively targets amyloid-β plaques, its overall clinical benefit appears less consistent when contrasted with alternative drugs employing different mechanisms of action.[43] In the light of promising results in preclinical and early clinical AD trials, AD patients were enrolled in two parallel phase 3 aducanumab trials, ENGAGE (initiated in August 2015) and EMERGE (initiated in September 2015). These studies were also designated as studies 301 and 302, respectively and had an identical design. In March 2019, the trials were halted after a futility analysis revealed little hope for treatment effectiveness. According to

the company *Biogen*, ENGAGE was not "trending positive" at the time of the futility study. However, EMERGE was and additional blinded data that were subsequently added by October of 2019 pushed EMERGE over the statistical threshold into significance for the high 10 mg/kg dose. According to *Biogen*, differences in the trials resulted from two protocol changes that permitted participants whose treatment had been interrupted due to ARIA to resume their prescribed dose and permitted participants with the APOE gene allele ε4 to switch from the 6mg/kg dose to the 10 mg/kg dose. These modifications would have exposed participants to greater antibody dosages. Biogen's claim that this increase would have benefited EMERGE differently since it began one month after ENGAGE does not provide a persuasive explanation for the disparate outcomes in the absence of actual data.[44]

The Phase 3 studies of aducanumab, EMERGE and ENGAGE, were global trials designed to validate the results of the Phase Ib trial in a larger number of subjects, evaluating aducanumab safety and efficacy in early-stage AD patients with amyloid pathology confirmed by PET tracers. Results were provided in 'abstract form' by Haeberlein and colleagues[45] during December 2020, based on the predetermined statistical analysis plan and the pre-planned futility analysis.

More specifically, the Phase 3 studies (EMERGE and ENGAGE) underwent a thorough analysis; both were deemed futile based on previously established futility standards. In this scenario, randomised clinical trials can incorporate interim analyses, with the opportunity to halt the investigation for futility should early data show insufficient promise of a treatment benefit. Such futility evaluation potentially reduces exposure of patients to an investigational treatment that may not be efficacious and saves research resources that may be better used for other studies. As described by Snapinn and colleagues, clinical trial sponsors,[46] in practice, do not necessarily feel bound by futility statistical stopping rules and boundaries and largely use them as non-binding guidelines rather than strict rules, thereby providing them flexibility. In the EMERGE and ENGAGE studies, futility analyses occurred on 50 % of patients completing 78 weeks of treatment. On incorporating complete patient data into the statistical analyses, the EMERGE investigation achieved its primary outcome measure (reducing cognitive decline as evaluated by the CDR-SB scale). This was corroborated by positive changes in secondary cognitive and functional measures in the EMERGE trial and the prior favourable CDR-SB change in the top aducanumab dose group from the prior PRIME clinical trial. To the contrary, the complete data set from the ENGAGE investigation did not exhibit a statistical change in CDR-SB score. Between late 2018, when data underwent futility analysis and March 2019, when the clinical trials were halted, a further 179 EMERGE and 139 ENGAGE patients finished their 18-month follow-up; thereby increasing the ultimate trial participant number to 982 and 1084, respectively. A noted key potential difference between the two clinical trials was that the EMERGE investigation had more patients who had received long-term (14 doses) of high-dose (10 mg/kg) aducanumab, as compared to the EMERGE trial. On evaluating participants in ENGAGE who were successfully administered comparable long-term high dosing as those in the EMERGE trial, similar treatment CDR-SB outcomes were noted, implying that total aducanumab exposure is an important factor and may account for the divergent treatment effects between the two clinical trials.

Chang et al. provides a comprehensive evaluation of statistical methods and practical considerations for futility stopping in clinical trials, emphasizing optimal timing and design of interim analyses to efficiently terminate ineffective treatments while minimizing the risk of stopping potentially beneficial ones.[47] Participants of EMERGE and ENGAGE were provided the opportunity to contribute to CSF biomarker sub-studies. From these smaller sub-studies, a statistically significant dose-dependent reduction in CSF phosphorylated tau (p-tau) and a trend (statistically insignificant change) towards a decline in total tau (t-tau) were noted.[48] These were accompanied by statistically significant reductions in tau PET SUVRs in key brain areas (temporal, medial temporal and frontal lobes). Significant time- and dose-dependent declines in amyloid PET SUVRs were also reported, as was a decline in plasma p-tau.[49] In the light of the amyloid hypothesis, whereby abnormal Aβ accumulation (and/or reduced Aβ clearance) triggers subsequent tau pathology and ensuing clinical decline, the authors involved in the EMERGE/ENGAGE studies interpreted the targeting of aggregated Aβ in the brain via aducanumab treatment and the corresponding changes in imaging and biochemical markers as having the potential to result in clinical benefit. In this scenario, the removal of

insoluble amyloid plaques and oligomers results in downstream effects on markers of p-tau and tau NFTs that can be construed as an aducanumab disease-modifying effect. The most frequent adverse action of aducanumab was ARIA, which was considered temporary and treatable by a titration regimen and safety monitoring with magnetic resonance imaging (MRI).[49]

Based on mechanism of action (MOA) and affinity investigations, the four drugs (aducanumab, BAN2401, gantenerumab and ALZ-801) have a relation with neurotoxic soluble Aβ oligomers in common that met all the requirements that are as follows: completed phase 3 or phase 2 studies in patients with symptomatic AD; proved adequate safety with a course of treatment that was less than 12 months, the legal minimum for long-term safety; reported significant impacts on AD imaging, clinical results, or fluid biomarkers; reported pharmacokinetic (PK) profiles and MOA clinically being developed actively.[50]

A case study of a 66-year-old white guy who was treated with aducanumab as part of the ENGAGE clinical trial and participated in a study that involved amyloid and tau PET. He suggested that amyloid-related imaging abnormalities with effusion or oedema (ARIA-E) and amyloid-related imaging abnormalities with hemosiderin deposits (ARIA-H) were found on MRI, along with acute symptoms such as headache and encephalopathy. Nicardipine and levetiracetam were used to treat epileptiform activity and malignant hypertension. A course of methylprednisolone was prescribed as a result of the subsequent clinical/imaging deterioration. In contrast to ARIA-H, symptoms and ARIA-E improved during six months. Interval amyloid PET quantitative analysis revealed decreased signal in pre-existing regions but an increasing posterior signal, whereas tau PET revealed an overall increased signal.[51]

CMS Chronic Condition Data Warehouse methods were used to identify adverse drug reactions and AD. The researcher determined MCI by looking for codes G3184 or R4181. Given historical discrepancies in clinical trial enrolment, the effects of sex, race and ethnicity were studied using characteristics from the CMS Master Beneficiary Summary File.[52] Experts also recommended some sources required for the use of aducanumab, are specified by Cummings.[53]

The researcher has evaluated the effectiveness of an aducanumab analogue (Adu), using APP23 mice in research with four treatment arms, comparing it to scanning ultrasound (SUS) and as a combo therapy and using a sham as a control. Spatial memory was evaluated using the active place avoidance (APA) test and amyloid was measured using histology and an enzyme-linked immunosorbent assay (ELISA) kit. The amount of brain antibodies was also measured.

The total deposit area in the hippocampus was shown to be decreased by both Adu and SUS and the treatment (SUS + Adu) had no additional impact. Only it produced a decrease in total plaque area. Only the SUS and SUS + Adu groups had animals whose plaque load was decreased from above 10 % to < 1 %. Just the SUS + Adu group showed significant memory improvement and 3 days after treatment, the level of Adu in this group was found to be 5 times higher than that in mice that only received Adu.

Together, these results imply that SUS is to be taken into account as a potential AD treatment. As an alternative, a combination study of Aducanumab and ultrasonography to increase antibody load in the brain may be necessary. Significant differences in behaviour and plaque burden are seen between APP23 mouse animals. The strain also has a mortality rate of more than 40 %, which made it difficult to get the large numbers of mice needed for the various treatments.[54] The findings of the study are represented in Figure 5.

In 2021, researchers presented a regulatory viewpoint on the subject and examined any parallels and discrepancies between the FDA's and European Medicines Agency's (EMA's) assessments. Participants with DIAD at both the symptomless and symptomatic disease stages received either gantenerumab or solanezumab. Although both medications have convincing Aβ targets, gantenerumab failed to have a good effect on cognitive tests during interaction and the group receiving solanezumab even displayed a higher cognitive deterioration compared to placebo on some tests.[55]

Hershey et al. critically evaluated aducanumab, highlighting limited and inconsistent clinical efficacy alongside notable safety concerns, and questioning whether amyloid reduction alone is an adequate surrogate endpoint for therapeutic benefit in Alzheimer's disease.[56] Ashique et al. provides a critical reappraisal of aducanumab,

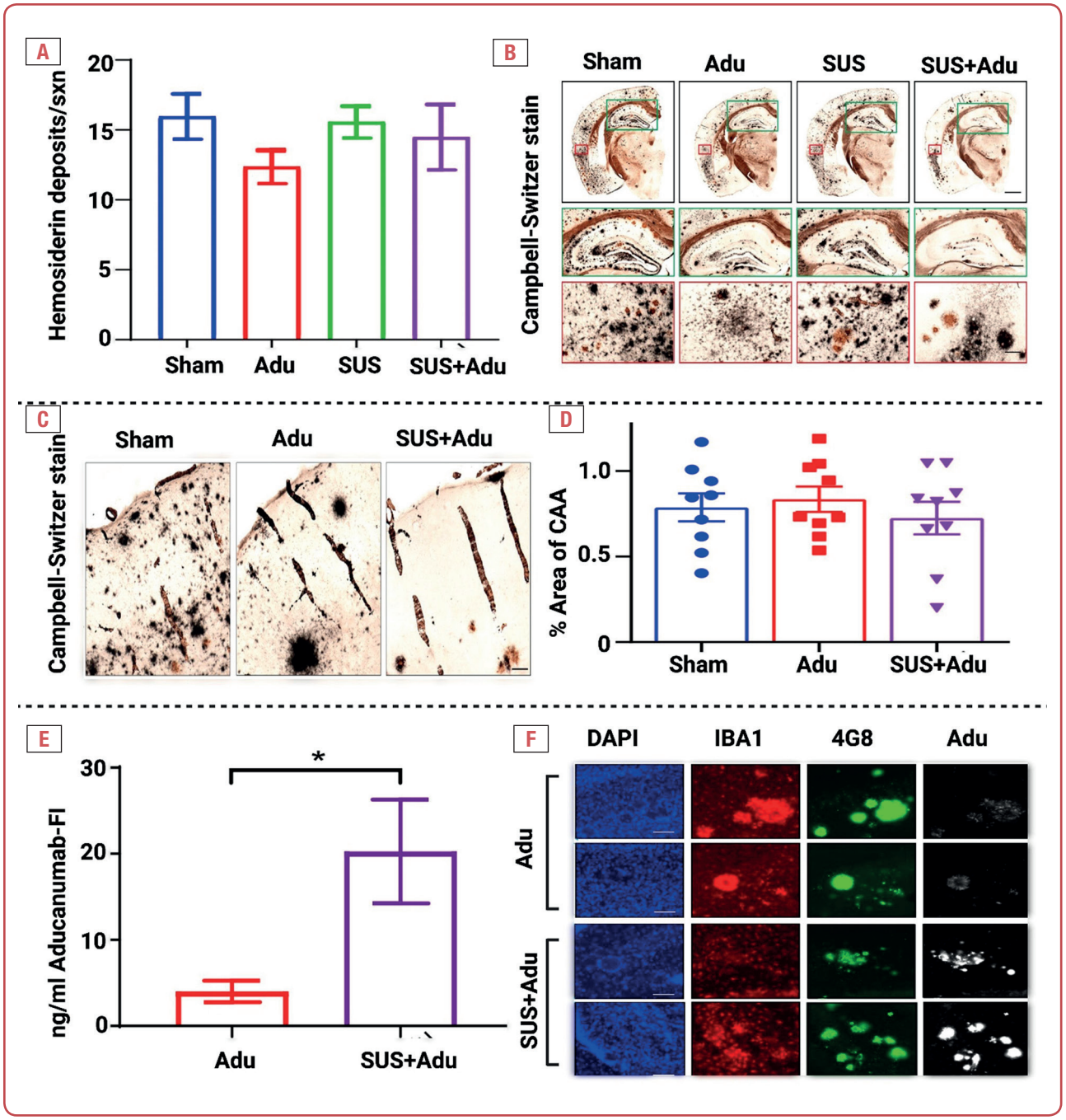

Figure 5: A: Aducanumab analogue (Adu), when dispensed by itself or with scanning ultrasound (SUS), shows no effect. B Treatment decreases deposits in APP23 mice. C Aducanumab does not affect cerebral amyloid angiopathy (CAA) or microhaemorrhages in APP23 mice. D Adu, when administered with or without SUS, did not affect CAA vessels. E: SUS raises the levels of sducanumab. F: Adu is detectable in the brain and visualised in the cortex and hippocampus. Reprinted from reference 54 under an open access license

underscoring its capacity to reduce amyloid burden while questioning the robustness and consistency of its clinical efficacy, and highlighting ongoing concerns related to safety, cost, and the uncertainty surrounding its overall benefit in Alzheimer's disease management. [57] The secondary study examined data from the EMERGE and ENGAGE, comparing doses of aducanumab treatment with placebo among individuals at 348 sites in 20 countries. These trials were double-blind, placebo-controlled, parallel-group, phase 3 randomised clinical trials. The trials' enrolment lasted from August 2015 to July 2018, but due to a futility analysis, they ended early. The total number of participants in the combined studies was 3285 and they all had AD. During the placebo-controlled period, they all received one or more doses of either aducanumab or a placebo. Additional analyses continued until July 2021, after the initial primary data analysis from November 2019

to July 2020. Once every four weeks, participants were randomly assigned to receive either high- or low-dose IV aducanumab or a placebo. A risk-reduction method adopted was dose titration.[58]

Scientists initially focused on mild to moderate AD, potentially at too advanced a stage. Later, with access to biomarkers, they discovered that nearly 30 % of patients lacked Aβ deposits. This led to the use of CSF and PET biomarkers to target early and mild AD defined by Aβ deposit, though drug dosages may have been insufficient. Eventually, consequences were observed with large dosages of aducanumab. Aducanumab received FDA approval on 7 June 2021.[59] Both its positive and negative impacts will significantly influence AD clinical research. The leadership of the ADNI, a large multisite longitudinal observational study to establish biomarkers for clinical trials, is reflected in this context. Numerous AD clinical trials, including the aducanumab investigations, have benefited from the design and statistical power of ADNI data.[60]

Huang et al. reviews recent clinical trials of novel Alzheimer's therapies, highlighting that anti-amyloid and anti-tau strategies, show incremental progress, achieving consistent clinical efficacy remains a major challenge, underscoring the need for earlier intervention and multi-target approaches.[61] On the other hand, Behl offers a collection of information highlighting both the strengths and shortcomings of aducanumab, while drawing global attention to the broader search for AD-modifying therapies. The failure of anti-amyloid strategies in AD has intensified efforts toward effective treatments. Behl's manuscript covers the timeline and effects of aducanumab in AD models, along with the controversial regulatory decision that followed. The paper offers a comprehensive discussion of the drug's mechanism and potential developments to improve both its acceptability and efficacy in AD treatment.[24] In addition, aducanumab's pharmacokinetics, pharmacodynamic properties, efficacy and safety trial data, regulatory consequences and future therapy directions are all outlined in another narrative review.[25]

In 2022, Haeberlein et al studied the safety and efficacy of aducanumab using phase 3 trials EMERGE and ENGAGE. Patients aged 50 to 85 years with confirmed amyloid pathology were enrolled. Approximately 1638 (EMERGE) and 1647 (ENGAGE) participants met the clinical criteria for MCI due to AD. Aducanumab was administered IV once every four weeks for 76 weeks in a 1:1:1 ratio (low dose, high dose, or placebo). The trials were terminated based on pre-specified data objectives. ENGAGE did not meet its primary or secondary outcomes and although EMERGE showed dose- and time-dependent reduction in amyloid pathology, the clinical benefit remained unclear.[45]

Although the EMERGE study was the first late-stage clinical trial of an amyloid-targeting drug that may have demonstrated efficacy, it remains uncertain whether aducanumab truly offers sufficient benefits to outweigh its drawbacks. Aducanumab does not meet widely accepted standards for cost-effectiveness and could place substantial strain on healthcare system budgets at its current pricing.[26] Clinical societies, regulators, manufacturers and patient organisations must work together to ensure fair access and pricing, especially given the massive unmet needs of AD patients and their families.

Recent studies

Recently, various clinical trial studies have been reported by different scientists.[62-64] Phase 2 studies of ABBV-916, CT1812 and varoglutamstat (VIVA-MIND) were also collected by Heidebrink.[62] In another reviews,[63-69] scientists concluded that, beyond the controversies, aducanumab has been the first drug targeting the AD pathological hallmark and has effectively reduced the clinical progression of the disease. However, it was only effective in the mild or early stages of AD. In 2024, focused ultrasound of three types of participants with several age difference and with each of six monthly aducanumab infusions to temporarily open the blood–brain barrier (BBB) to enhance amyloid removal in selected brain regions in three participants over 6 months, resulted in a greater reduction in the level of Aβ than aducanumab therapy alone in homologous regions was reported.[57, 65, 70] The signalling pathways and molecular mechanisms through which aducanumab effectively prevents disease pathogenesis in AD were reported.[71-73] The drug development of AD is compiled by Cummings.[74, 75] They included all clinical trials assessing pharmaceutical therapies for AD active from 1 January 2024. They used the Common Alzheimer's Disease Research Ontology

Table 2: Showing the phase 3 clinical trial data of aducanumab

Agent	Dose	Type	Company	Objective	Therapeutic purpose	Status
Aducanumab (EMBARK)	10 mg/kg IV	Phase-3	*Biogen*	To evaluate the long-term efficacy of aducanumab	Immunotherapy (passive)	Active, not recruiting [78]
Aducanumab (ENVISION)		Phase-3	*Biogen*	To evaluate the safety and efficacy of	Immunotherapy (passive)	Recruiting [79-81]
Aducanumab (ADUHELM)	100 mg/mL IV	Phase-3	*Biogen*	To clear amyloid plaques	Immunotherapy (passive)	Approval accelerated [82-84]
EMERGE	10 mg/kg IV	Phase-3	*Biogen*	To evaluate the safety and efficacy of aducanumab	Immunotherapy (passive)	Approved [85, 86]
EMERGE	10 mg/kg IV	Phase-3	*Biogen*	To evaluate the safety and efficacy of aducanumab	Immunotherapy (passive)	Approved [82, 87]

(CADRO) to classify the targets of therapies in the pipeline. There are 164 trials assessing 127 drugs across the 2024 AD pipeline. There were 48 trials in Phase 3 testing 32 drugs, 90 trials in Phase 2 assessing 81 drugs and 26 trials in Phase 1 testing 25 agents. Of the 164 trials, 34 % (N = 56) assess disease-modifying biological agents, 41 % (N = 68) test disease-modifying small molecule drugs, 10 % (N = 17) evaluate cognitive enhancing agents and 14 % (N = 23) test drugs for the treatment of neuropsychiatric symptoms.

In another study by Bayesian[76, 77] random effects meta-analysis was used to quantify evidence for or against a treatment effect and assessed the size of the effect and its heterogeneity. Data were extracted from published studies where available and web-based data reports, assuming a Gaussian data generation process. Authors have found moderate evidence in favour of a treatment effect (Bayes factor = 13.2). The effect was moderate to small with −0.33 (95 % credible interval −0.54 to −0.10) points on the CDR-SB scale. The heterogeneity parameter was low to moderate with 0.21 (0.04 to 0.45) CDR-SB points. The unique intraneuronal actions of two FDA-approved monoclonal antibodies, aducanumab and lecanemab, were studied and provide a reliable and accessible human neuronal model for evaluating potential AD therapeutics, emphasising the importance of intraneuronal pathology in the treatment of AD. Compiled phase 3 clinical data of aducanumab is shown in Table 2.

Conclusion

The primary pathology of AD is amyloid deposition, which is the focus of the medication aducanumab, as well as tau abnormality. It is a promising path for a progressive condition with few effective treatments; however, the foundation for this "promise" is built on contradictory findings. In all of the clinical trials and the various dose groups, the clinical improvement is not consistently discernible. Moreover, a high dose of aducanumab has been linked to higher side effects like ARIA. Also, some debates have been sparked by the contradictory results of aducanumab's clinical trials. The requirement for ongoing brain imaging monitoring, the lack of cost-effectiveness and the uncertainty surrounding long-term efficacy are all significant problems. Recognising the available data is a critical first step, but gaining a more thorough scientific understanding is also crucial. Aducanumab could not be the "exclusive" treatment for AD pathology and any new medication is sure to spark controversy. A novel chemical approved for the early stages of a fatal neurodegenerative illness like AD sparks caution and hope simultaneously outside of the academic and economic conversation. Given the severity of the condition, disease-modifying therapies for AD are of utmost importance; therefore, scientific research should concurrently focus on identifying all potential pathogenic processes and developing the necessary medications, including but not restricted to aducanumab.

In this context, AD progression is driven by a tightly interlinked cascade involving TREM2 dysfunction, mitochondrial impairment and oxidative stress. Dysfunctional TREM2 attenuates microglial activation and amyloid β clearance, contributing to prolonged neuroinflammation. Mitochondrial deficits—including compromised bioenergetics, altered dynamics and impaired mitophagy—reduce ATP production while increasing reactive oxygen species (ROS), a phenomenon increasingly recognised as a core early event in AD pathogenesis. Concurrently, oxidative stress damages lipids, proteins and nucleic acids, reinforcing mitochondrial dysfunction and amplifying amyloid and tau pathologies in a self-propagating loop. Collectively, these mechanisms form a vicious cycle that exacerbates neuronal dysfunction and cognitive decline, underscoring the necessity of therapeutic strategies aimed at restoring TREM2-mediated microglial function, preserving mitochondrial health and mitigating oxidative damage.

List of abbreviations

bCFT: Membrane-bound fragment; a-CTF: C-terminal fragment. A.A: amino acid; AD: Alzheimer's disease; ADAS-cog: Alzheimer's Disease Assessment Scale—cognitive subscale; ADCOMS: Alzheimer's Disease Composite Score; AICD: Amyloid precursor protein intracellular domain; APOE: Apolipoprotein E; APP: Amyloid precursor protein, ARIA: Amyloid-related imaging abnormality; ARIA-E: Amyloid-related imaging abnormalities with effusion or edema; ARIA-H: Amyloid-related imaging abnormalities with hemosiderin deposits; Aβ: amyloid-β; BBB: Blood brain barrier; CDR-SB: Clinical Dementia Rating—Sum of Boxes; CSF: cerebrospinal fluid; DIAN-TU: Dominantly Inherited Alzheimer's Network Trials Unit; FDA: Food and Drug Administration; Ig: immunoglobulin; IV: Intravenous; MCI-AD: Mild cognitive impairment due to Alzheimer disease; MOA: Mechanism of action; MRI: Magnetic resonance imaging; Nfc: Neurofilament light chain; NFTs: Neurofibrillary tangles; PET: Positron emission tomography; PHF: Paired helical filaments; PK: Pharmacokinetic; p-Tau: phospho-Tau; sAPPa: Soluble Amyloid precursor protein released by a-secretase;sAPPβ: Soluble Amyloid precursor protein released by β-secretase; SC: Subcutaneous; SUVR- standard uptake value ratio t1/2: Half-life; t-tau: Total tau.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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