ΝΟΣΟΤΡΟΠΟΠΟΙΗΤΙΚΕΣ ΑΝΤΙ-ΑΜΥΛΟΕΙΔΙΚΕΣ ΘΕΡΑΠΕΙΕΣ ΓΙΑ ΤΗΝ ΗΠΙΑ ΝΟΗΤΙΚΗ ΔΙΑΤΑΡΑΧΗ Η/ΚΑΙ ΤΟ ΗΠΙΟ ΣΤΑΔΙΟ ΑΝΟΙΑΣ: ΑΡΘΡΟ ΑΝΑΣΚΟΠΗΣΗΣ ΤΩΝ ΚΥΡΙΑΡΧΩΝ ΚΛΙΝΙΚΩΝ ΜΕΛΕΤΩΝ ΦΑΣΗΣ ΙΙΙ

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ΠΕΡιΛΗΨΗ

Η νόσος Alzheimer είναι η πιο συχνή αιτία άνοιας, μια νευροεκφυλιστική διαταραχή η οποία προσβάλλει κατά βάση τους ηλικιωμένους και της οποίας ο επιπολασμός αυξάνει καθώς ο παγκόσμιος πληθυσμός γηράσκει. Η καθ' υπεροχήν εξασθένηση της πρόσφατης μνήμης είναι μια κυρίαρχη κλινική εκδήλωση της AD, στην αρχή τουλάχιστον, αν και υπάρχουν εξαιρέσεις, και η βασική παθολογία της νόσου αποτελείται από τη συσσώρευση πλακών β-αμυλοειδούς. Η συσσώρευση του β-αμυλοειδούς αντανακλάται και μέσω των βιοδεικτών (Αβ42, Αβ42/Αβ40), των οποίων τα επίπεδα μεταβάλλονται σχεδόν 19 με 15 χρόνια πριν από την έναρξη των συμπτωμάτων, σύμφωνα με την πορεία της νόσου η οποία αποτυπώνεται σε αρκετές μελέτες ακόμη και στις μέρες μας. Ως απόκριση στην παθολογική αναδίπλωση του β-αμυλοειδούς, έχουν δοκιμαστεί πολλές νέες θεραπείες με στόχο αυτό το παθολογοανατομικό υπόστρωμα, σε αντίθεση με τις αποδεκτές διαθέσιμες θεραπείες, από ετών, οι οποίες μπορούν να βελτιώσουν ορισμένα συμπτώματα μόνο, ενώ η ασθένεια εξελίσσεται αναπόφευκτα. Αυτό το κείμενο είναι ένα άρθρο ανασκόπησης των τριών μονοκλωνικών αντισωμάτων τα οποία έδειξαν μία κάποια αποτελεσματικότητα έναντι του β-αμυλοειδούς, του aducanumab, του lecanemab και του donanemab, και των σχετικών κλινικών δοκιμών φάσης III, ως προς το σχεδιασμό, τα κύρια χαρακτηριστικά, το προφίλ ασφάλειας και τα αποτελέσματα. Το τελευταίο μονοκλωνικό αντίσωμα έλαβε πρόσφατα έγκριση από τον Οργανισμό Τροφίμων και Φαρμάκων (FDA) και βρίσκεται υπό αξιολόγηση από τον Ευρωπαϊκό Οργανισμό Φαρμάκων (EMA), ενώ το aducanumab και το lecanemab έχουν ήδη εγκριθεί από τον FDA, και προσφάτως το lecanemab και από τον EMA. Υπογραμμίζουμε επίσης πολλά βασικά σημεία και κενά των συγκεκριμένων κλινικών μελετών και παρέχουμε πτυχές της συνεχιζόμενης έρευνας.

Λέξει-κλειδιά: νόσος Alzheimer, μονοκλωνικά αντισώματα, συσσώρευση β-αμυλοειδούς, κλινικές μελέτες

DISEASE MODIFYING ANTI-AMYLOID THERAPIES FOR MILD COGNITIVE IMPAIRMENT / MILD ALZHEIMER'S DISEASE: A NARRATIVE REVIEW OF THE KEY PHASE III CLINICAL TRIALS

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ABSTRACT

Alzheimer's disease is the most common cause of dementia, a neurodegenerative disorder of older adults primarily, which is rising as the world population ages. Selective memory impairment is a prominent clinical manifestation of AD, although there are exceptions, and the core disease pathology consists of

amyloid aggregation. The amyloid positivity is also reflected through the biomarkers ($A\beta_{42}$, $A\beta_{42}/A\beta_{40}$) that appear firstly changed, almost 19 to 15 years prior to symptoms, according to the disease trajectory which is confirmed by several studies even nowadays. In response to amyloidosis, plenty of novel therapies have been tried out and target the amyloid accumulation, contrary to the accepted available treatments which can improve some symptoms, while the disease inevitably progresses. This current article provides an overview of the three successful monoclonal antibodies against amyloid aggregates, aducanumab, lecanemab, and donanemab, and their relevant phase III clinical trials as for design, main characteristics, safety profile and outcomes. The latter one has been recently accepted by Food and Drug Administration (FDA) and is under evaluation of European Medicines Agency (EMA), though aducanumab and lecanemab have already been FDA approved, and only lecanemab has been recently EMA approved. We also underline several key points and gaps of current evidence and provide aspects of ongoing research.

Keywords: Alzheimer's disease, monoclonal antibodies, amyloid aggregations, clinical trials

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease, accounting for 60 – 70% of all dementia cases.[1] Usually, adults present with symptoms in mid to late life and apart from the common amnestic, different other clinical phenotypes have been recognised, including posterior cortical atrophy, logopenic variant primary progressive aphasia (PPA), corticobasal syndrome and frontal subtypes.[2] The pathophysiological hallmark of the disease is the extracellular aggregation of β-amyloid, in the form of amyloid plaques and the intracellular aggregation of hyperphosphorylated tau protein, in the form of neurofibrillary tangles.[3] In this biological context, the National Institute on Aging and Alzheimer's Association (NIA-AA) research framework, in 2018,[4] introduced a biological definition of the disease, through a classification scheme labelled AT(N), revised in 2024,[5] and since then AD is diagnosed and staged ***in vivo*** based on specific biomarker profiles in conjunction. Mounting evidence has already established the application of advanced neuroimaging techniques,[6] including amyloid and tau positron emission tomography (PET) and/or cerebrospinal fluid (CSF) biomarkers,[7] which are broadly used in clinical trials, whilst plasma biomarkers are expected to be validated and subsequently commonly used, according to the revised AD criteria.[5]

The current treatment scheme consists of therapies that offer partial symptomatic relief without halting the disease's progression and without targeting the underlying pathological burden or the neuroinflammation that has been already proved to contribute to AD pathogenesis.[8] Currently, many substances are being evaluated in clinical trials and, for instance, efforts are underway to study the efficacy of semaglutide in mild cognitive impairment (MCI) and/or mild AD, taking into consideration that glucose metabolism is associated with the pathogenetic mechanism of AD, as supported by recent studies.[9,10] Until recently, disease modifying treatments were not available. However, several recent developments of anti-amyloid monoclonal antibodies (mAbs), years in the pipeline, emerged although with variance in efficacy and adverse events. Bapineuzumab,[11] gantenerumab,[12] solanezumab,[13] and crenezumab[14] are examples of these mAbs that did not succeed in reducing cognitive decline, in comparison to others which showed statistically significant results in clinical trials. In June 2021, aducanumab was the first anti-amyloid antibody approved by FDA in the USA using the accelerated approval pathway, followed by lecanemab which has been fully FDA approved by the traditional pathway and also licensed by EMA, after re-assessment in November 2024. Donanemab is the third one that has been recently approved by the FDA. The present article summarises the key phase III clinical trials of the aforementioned approved monoclonal antibodies as for design, main characteristics, safety profile and outcomes. We also underline several crucial points and gaps of current evidence and provide aspects of ongoing research.

FUNCTIONS AND RATIONALE BEHIND THE IMMUNOTHERAPY DRUGS AGAINST AB

Alzheimer's disease is a complex neurodegenerative disease that has a prolonged preclinical phase of 10-30 years duration, during which the underlying biochemistry/pathology progresses but individuals remain cognitively unimpaired [15]. Multiple studies have demonstrated the continuum of disease pathology, identifying that CSF and plasma biomarkers, which reflect or are triggered by amyloidosis, were detected 15 to 19 years prior to symptom onset [16]. Amyloidosis is expressed through decreased plasma and CSF Aβ42, and Aβ42/Aβ40 or positive amyloid PET scan, whilst increased levels of CSF or plasma phosphorylated tau (p-tau) protein 181 or 217 are triggered by amyloidosis.[17] The three mAbs differ in the type and range of amyloid species targeted (Figure 1). More specifically, aducanumab addresses a broad range of amyloid species with a greater affinity of high molecular weight ones, and especially fibrils; lecanemab targets the soluble protofibrils;

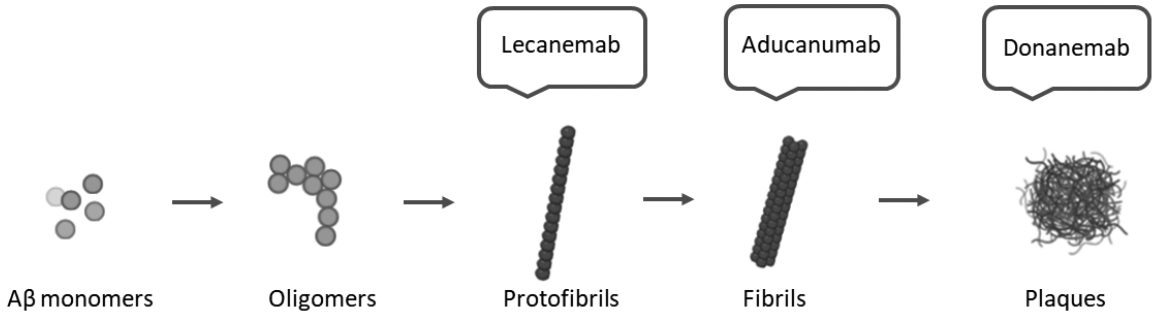

Figure 1: Monoclonal antibodies against specific targets of aggregated β-amyloid.

and donanemab is directed against insoluble plaques only.[18] All mAbs were implemented for MCI/mild AD and are immunoglobulins (Ig) G1 antibodies and their mechanism of action is the reduction of amyloid plaques through solubilization of Aβ and the activation of microglia with phagocytosis of Aβ fibrils via the endosomal / lysosomal system.[19] It is uncertain if these activated microglia can phagocytose both labelled and unlabelled protein aggregates, and if they could be directed to tau aggregates despite their intracellular location, because there is evidence that plasma ptau also responses to mAbs administration.[20] In addition to phagocytosis, complement activation promotes microglial uptake and surprisingly, there are other non-microglial mediated mechanisms for Aβ clearance. "Peripheral sink" activity has been described, for example, and refers to the action of mAbs through the peripheral blood inducing the efflux of Aβ aggregates via the blood brain barrier (BBB). Low density lipoprotein receptor-related protein 1 (LRP1) plays a major role in this mechanism.[21]

Aducanumab

Aducanumab is the first disease modifying therapy (DMT) for AD that received accelerated approval from the FDA on June 7, 2021.[22] Two phase 3 randomised double blind placebo-controlled trials, EMERGE and ENGAGE,[23] evaluated the efficacy and safety of aducanumab in patients with MCI or mild symptomatic AD. Participants of these two trials were 50-85 years old and were randomised 1:1:1 to aducanumab low dose, high dose, or placebo (Table 1) via intravenous infusion every 4 weeks. The major inclusion criteria were a Mini Mental State Examination (MMSE) score of 24 to 30 and the confirmation of amyloid pathology with amyloid PET (Table 2). The primary endpoint was the change in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) from baseline until the week 78 and the secondary ones were other commonly used neuropsychological scales (Table 2) accompanied by the mean change of the cortical composite standardised uptake value ratio (SUVR) in the amyloid PET. The primary endpoint was not met in

Study	Antibody	Company	Dose		Sample size			Age	Dosage protocol / Duration
Haeberlein et al. 2022 (EMERGE)	aducanumab	Biogen, Neurimmune	3 mg/kg or 6 mg/kg	10 mg/kg	543	547	548	50 - 85	Every 4 weeks iv / 76 weeks
Haeberlein et al. 2022 (ENGAGE)	aducanumab	Biogen, Neurimmune	3 mg/kg or 6 mg/kg	10 mg/kg	547	555	545	50 - 85	Every 4 weeks iv / 76 weeks
van Dyck et al. 2023 (CLARITY AD)	lecanemab	Eisai, BioArktic, Biogen	10 mg/kg		859	875		50 - 90	Every 2 weeks iv / 18 months
Sims et al. 2023 (TRAILBLAZER – ALZ 2)	donanemab	Lilly	700 mg for the first 3 doses and 1400 mg thereafter		860	876		60 - 85	Every 4 weeks iv / 76 weeks

Table 1. Phase III trials features and baseline characteristics of participants.
The participants in EMERGE and ENGAGE trials were randomised (1:1:1) to receive low-dose aducanumab, high-dose aducanumab, or placebo. The three columns of sample size concerning these studies correspond to low dose, high dose, and placebo group respectively.
iv: intravenously.

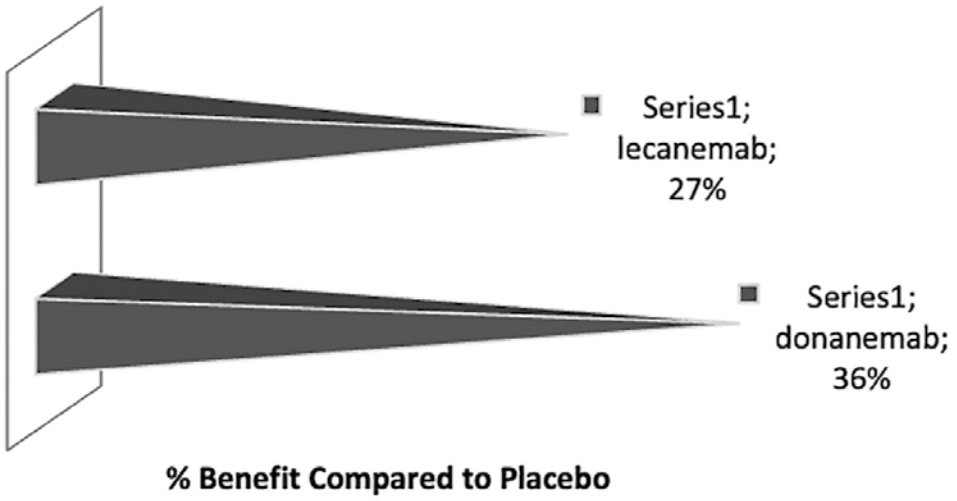

Figure 2: % Benefit of mAbs lecanemab and donanemab compared to placebo in CDR-SB, based on CLARITY-AD and TRAILBLAZER-ALZ 2, respectively.
CDR-SB: Clinical Dementia Rating - Sum of Boxes

ENGAGE trial while the high dose group in EMERGE experienced less worsening in mean CDR – SB than the placebo group (Table 3), without even reaching the clinically important threshold for CDR-SB change. [24] However, even in the unsuccessful ENGAGE trial, post hoc analysis data – limited to subjects exposed to the 14 sets of infusions- revealed also an interesting impact on CDR-SB in the high dose ENGAGE arm.[25] As for safety issues, Amyloid Related Imaging Abnormalities (ARIA) refers to radiological findings accounted to vasogenic oedema (ARIA-E) and/or haemorrhagic lesions, acute or chronic, (ARIA-H). [26] Of particular note, APOE ε4 carriers and participants of high dose group were mainly susceptible to ARIA but in the great majority of almost all cases symptoms were manageable and resolved within 4 months (83%). These symptoms are not identical and include predominantly headache, dizziness, nausea, and confusion.[27]

On January 31, 2024, it was announced by the corresponding company (Biogen) that aducanumab 100 mg/mL injection for intravenous use would not be at disposal anymore and this decision was not associated to any safety concern.[28]

Lecanemab

Consequently, lecanemab, initially approved through the accelerated approval pathway by the FDA, is the first mAb against Aβ aggregates, which was granted traditional approval, on July 6, 2023,[29] following the deliberation of the CLARITY AD study. [20] Almost one year later, on 14 November 2024, EMA issued the consent of lecanemab's marketing authorisation, after re-examination, suggesting that the benefit could overwhelm the risk of the adverse events, and especially ARIA, for individuals with one or no copy of ApoE4.[30] CLARITY AD, the aforementioned confirmatory trial, was an 18-month, multicentre, double-blind, placebo-controlled, parallel-group trial in patients aged 50 to 90 years with either MCI or mild AD (Table 1). Eligible subjects were assigned in a 1:1 ratio to receive lecanemab, 10mg/kg intravenously every 2 weeks, or placebo, and they scored over 22 in MMSE, while amyloid positivity was obtained through amyloid PET or CSF $A\beta_{42}$ (Table 2). An effort was made to broaden the study population, including, for example, non-White participants (20%) and patients under anticoagulation therapy if the dose was stable at least 4 weeks before screening. The mean change of CDR-SB was the primary end point. Secondary end points included a new scale that is called Alzheimer's Disease Composite Score (ADCOMS).[31] This score consists of several items of other already used scales, and in particular of Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), MMSE, and CDR-SB (Table 4) and it has been proposed as an outcome measure of prodromal AD with increased sensitivity.[31] Even though a clinically meaningful effect in the mean CDR-SB score was not observed, lecanemab accomplished statistically significant changes in CDR-SB, resulting in a 27% delay of disease progression (Figure 2). This result is consistent with the efficacy in reducing the amyloid burden on PET, about 55.5 in centiloid scale, and it has an effect of 4 to 6 months on slowing disease progression when added to existing therapy,[32] raising question as to whether is meaningful or not.[30]

During the study period, the safety results included infusion reactions (>10%) and ARIA-H and ARIA-E (Table 3), but the overall percentages were lower than those observed in aducanumab trials, again

Study	Clinical eligibility criteria	Radiological eligibility criteria	Primary endpoint	Key Secondary endpoint
Haeberlein et al. 2022 (EMERGE)	CDR 0.5 MMSE ≥ 24 RBANS ≤ 85	Positive amyloid PET scan, brain MRI with ≤ 4 microbleeds, ≤ 1 lacunar infarct, without any prior ICH cortical infarct, severe white matter disease or superficial siderosis	CDR - SB	MMSE, ADAS-Cog13 and ADCS-ADL-MCI
Haeberlein et al. 2022 (ENGAGE)	CDR 0.5 MMSE ≥ 24 RBANS ≤ 85	Positive amyloid PET scan, brain MRI with ≤ 4 microbleeds, ≤ 1 lacunar infarct, without any prior ICH, cortical infarct, severe white matter disease or superficial siderosis	CDR - SB	MMSE, ADAS-Cog13 and ADCS-ADL-MCI
van Dyck et al. 2023 (CLARITY AD)	CDR 0.5 1 standard deviation below age-adjusted mean in the WMS-IV LMII MMSE ≥ 22	Positive amyloid PET scan#, brain MRI with ≤ 4 microbleeds, ≤ 1 lacunar infarct, without any prior ICH, stroke involving a major vascular territory, severe white matter disease or superficial siderosis	CDR - SB	PET – SUVR, ADCOMS, ADAS-Cog14
Sims et al. 2023 (TRAILBLAZER – ALZ 2)	20 < MMSE < 28	florbetapir F18 PET, flortaucipir F18 PET, brain MRI with ≤ 4 microbleeds, > 1 area of superficial siderosis, without any prior ICH or severe white matter disease	iADRS	ADAS-Cog13, ADCS-iADL, CDR-SB and MMSE

Table 2. Main characteristics of trials' design and endpoints.

CDR: Clinical Dementia Rating; MMSE: Mini Mental State Examination; RBANS: Repeatable Brief Assessment of Neuropsychological Status; WMS-IV LMII: Wechsler Memory Scale IV-Logical Memory (subscale) II; PET: Positron Emission Tomography; MRI: Magnetic Resonance Imaging; ICH: intracerebral haemorrhage; SB: Sum of Boxes; ADAS-Cog13: Alzheimer's Disease Assessment Scale–Cognitive Subscale 13 items; ADCS-ADL-MCI: The Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale for use in Mild Cognitive Impairment; iADRS: The Integrated Alzheimer's Disease (AD) Rating Scale; SUVR: standard uptake value ratio; ADCOMS: The Alzheimer's Disease Composite Score.

#Amyloid positivity could also be determined through CSF measurement of $A\beta_{1-42}$.

with higher frequency in ApoE ***ε4*** homozygous participants. Within the lecanemab group, the symptomatic subjects with ARIA-E were 2.8% and with ARIA-H were 0.7%. During this core study, there were 6 deaths in lecanemab arm, unrelated to the treatment without surpassing placebo, but, during the open-label extension (OLE) study (18-48 months), 4 deaths were attributed to lecanemab and two of them occurred due to intracerebral haemorrhage (ICH).[33]

Donanemab

The third anti-amyloid antibody which was recently fully approved by the FDA, on 2nd July 2024 (34), through the promising results of TRAILBLAIZER-ALZ2 (35), is the donanemab and targets the insoluble amyloid plaques in the brain (Figure 1). The main trial design and duration is similar to CLARITY AD but there are major distinguishing features. The participants, aged 60 to 85 years, with mild dementia or MCI, scored between 20 to 28 on MMSE and were further subdivided into groups according to tau PET scan, low/medium or high tau. Therefore, it was en-

Study	Adjusted mean difference from placebo in CDR-SB in 18 months		Adjusted mean change from baseline in amyloid PET (centiloid scale)		ARIA - H	ARIA - E
Haeberlein et al. 2022 (EMERGE)	-0.39 (-22%)#		-71%#		44%#	35%#
Haeberlein et al. 2022 (ENGAGE)	0.03 (2%)#		-59%#		42%#	36%#
van Dyck et al. 2023 (CLARITY AD)	- 0.45		- 55.48		17.3%	12.6%
Sims et al. 2023 (TRAILBLAZER – ALZ 2)	-0.67¥	-0.70§	-88¥	-87§	31.4%	24%

Table 3. Phase III trials outcomes.
Negative percentage means less progression (CDR-SB) in the treated arm and decrease in centiloid scale.
CDR-SB: Clinical Dementia Rating - Sum of Boxes; PET: Positron Emission Tomography; ARIA: Amyloid Related Imaging Abnormalities; -H: haemorrhage; -E: oedema/effusion.
#high dose aducanumab; ¥in the low/medium tau population; §in the combined population.

sured an accurate diagnosis of AD, beyond amyloid positivity appropriately for the diagnostic criteria of the disease.[4,5] Another differentiating point is the primary outcome (Table 2) of this trial which is the integrated Alzheimer's Disease Rating Scale (iADRS), a sensitive instrument in capturing treatment group differences in trials. This combines ADAS-Cog14 and ADCS-iADL, as a composite score of both cognition and functional status (36,37), as shown below:

iADRS = [-1 ADAS-Cog14 + 90] + ADCS-iADL

At 18 months, amyloid centiloid scale decreased by 88 in the low/medium tau population and it is noteworthy that almost 50% of the participants met the completion criteria of the study as for amyloid clearance (centiloids < 11), and discontinued the treatment. The slowing of clinical progression reached 36% for CDR-SB in the low/medium tau population (Figure 2) and 28.9% in the combined population, a clinically meaningful result regardless of statistical model. These percentages reflect a delay in cognitive decline by 7.53 months in the low/medium tau population and 5.44 months in the combined population.[38] Furthermore, as a downstream effect of amyloid plaque clearance, the examined plasma biomarkers were markedly decreased, especially plasma p-tau 217, instead of p-tau 181 used in CLARITY AD. This effect was not equivalent to tau SUVR which didn't show any significant difference during the 76 weeks. As expected, ARIA-H and ARIA-E were unavoidable (Table 3) but independent to antithrombotic use with at least half of cases (57.9%) occurring within the first three infusions of donanemab.

CRITICAL CONSIDERATIONS

The use of anti-amyloid monoclonal antibodies has attracted worldwide attention but requires careful consideration, taking into account the following special concerns. Initially, strict extrapolation of clinical trial criteria to real-world populations may limit the patients which could be benefited, since participants were free of some of the most common comorbidities (eg stroke or seizures within 12 months before randomisation) whilst even the concomitant use of specific medication could be an obstacle of their eligibility. Furthermore, the proportion of Black or Hispanic participants was unequivocally lower than White patients (approximately 91.5%). Actually, there are certain subgroups of AD patients who are excluded by DMTs' administration, such as patients with mixed pathologies, significant visual problems (posterior cortical atrophy (PCA)), behavioural and other atypical presentations, younger age, and inherited AD. The latter category also encompasses Down syndrome population which represents a genetic form of AD with complete penetrance of AD pathology by the age of 30 years and dementia by 45 to 50 years.[39,40]

A meaningful consideration is about the subsequent handling of these patients in regard to ARIA, beyond the examined 18 months duration of these clinical trials. It has to be clarified the complete reversibility of ARIA and this is critical, mainly, because lots of cerebrovascular events are not unusual in real-world aging population and the emergent therapies may be harmful. This is the unfortunate example of one patient, being on the lecanemab arm of CLARITY AD, who died from intracerebral haemorrhage following tissue plasminogen activator due to ischemic stroke and the autopsy revealed cerebral amyloid angiopathy (CAA).[41] Another important point that poses a question is the feasibility of amyloid clearance preservation and the duration of this outcome. As for the amyloid clearance, it is crucial to reconsider the physiological functions of amyloid and realise if the more beneficial effects of donanemab in CDR-SB

Scale	Item Name
ADAS-Cog	Delayed word recall
	Orientation
	Word recognition
	Word-finding difficulty
MMSE	Orientation to time
	Drawing
CDR-SB	Personal care
	Community affairs
	Home and hobbies
	Judgment and problem solving
	Memory
	Orientation

Table 4. Alzheimer's Disease Composite Score (ADCOMS)
ADAS-Cog: Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE: Mini Mental State Examination; CDR-SB: Clinical Dementia Rating-Sum of Boxes.

are due to treatment interruption in case of massive decrease of amyloid plaques in order to avoid the excess removal of the soluble Aβ species. In addition, it is required careful study to discover any association between the amyloid removal and the whole brain volume loss that was noticed by these trials.[42]

Regarding the unsuccessful studies of several mAbs and the intended CDR-SB reduction over 30%, it is debatable if this magnitude of response reflects a clinical meaningful change.[43] The magnitude of the acceptable drug-placebo difference is dependent also on the cognitive scoring tool used, so there are thresholds for ADAS-Cog, MMSE etc, accordingly. The FDA has stated the minimal clinically important difference (MCID) which is a clinician anchored threshold and has not been met in any scale involved in these three key clinical trials.[44] First of all, this estimate differs between mild AD and MCI, with lower sensitivity of change of CDR-SB in the latter one, explaining partially smaller effects of trials containing higher number of participants with MCI.[45] The families, patients, and clinical doctors do not perceive the positive outcome, >30% decrease of CDR-SB, because of the lack of improvement above baseline.[42] In fact, this degree is equivalent to a prolongation of the MCI phase by approximately 7.5 months. It is expected that upcoming mAbs may increase the difference between treatment and no treatment arm. Finally, except the clinical, there is also the biological threshold of achievement and is based on β-amyloid clearance, expressed through centiloids in amyloid PET, and this cut off value is established in 25 centiloids. Levels of β-amyloid above 25 centiloids. Remaining levels of β-amyloid above 25 centiloids foreshadow unsuccessful results in clinical progression, irrespective of total amount of amyloid clearance achieved.[42]

The cornerstone of the limitation of the clinical use of these mAbs is the cost, which has already been of great concern in the research community.[46] Indicative parameters of the aforementioned limitation are the cost of detecting the eligible patients, the nosocomial dependence for the intravenous infusion, the strategic stuffing of these healthcare facilities and the multiple follow-up magnetic resonance imaging (MRI). Accordingly, the pricing policy of lecanemab,[46] for example, hasn't been determined in Europe and it is remarkably difficult to estimate the pharmaceutical expenditure, especially since the estimate of the number of targeted population cannot be accurate in some countries without well-established registries. Furthermore, the current cost, may be unsustainable for the economy of the European Union[46] and the potential extrapolation to reimbursement models, resembling Medicare and Veterans Health Administration USA, could raise concerns for inequality in public health access which is discordant to the standards of at least some of the European countries.

Moreover, in the light of the urgency of early detection of affected individuals, with less invasive and less costly techniques, plasma biomarkers have emerged as useful tools in AD diagnosis and following progression or treatment response. Among these, ptau 217 has gained a place in diagnostic criteria[5] since it has been suggested to have a decent diagnostic accuracy.[47,48]

CONCLUSIONS

In general, there have been tested several mAbs and plenty of them did not succeed in reaching the curative effect on functional and cognitive symptoms of AD patients,[49] and at the same time, many efforts have failed with anti-tau monoclonal antibodies.[50] However, there are many encouraging results that are anticipated by ongoing clinical trials, such as subcutaneous formulation of lecanemab and Trailblazer-ALZ 3, a trial with innovative design targeting cognitively unimpaired participants.[51] Additional evidence is needed in order to provide the appropriate therapy to our patients, with realistic expectation, safety and convenience. Nevertheless, anti-amyloid mAbs have revolutionised therapeutic development, leading to a new era of AD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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