BRAIN
UPDATE

Anti-amyloid antibody therapies in Alzheimer's disease

Robert Perneczky,[1,2,3,4,5] Frank Jessen,[6,7,8] Timo Grimmer,[9] Johannes Levin,[2,3,10] Agnes Flöel,[11] Oliver Peters[12,13,†] and Lutz Froelich[14,†]

[†]**These authors contributed equally to this work.**

After years of failed attempts to develop a disease-modifying therapy for Alzheimer's disease, consistent evidence in support of clinical efficacy was finally presented for a monoclonal antibody targeting the amyloid-β protofibrils. In addition to meeting the primary outcome of slowing clinical disease progression over 18 months, secondary clinical outcomes and amyloid-β lowering on PET also underpin the positive results of the trial.

In this opinion piece, we highlight the key characteristics of the previous unsuccessful trials and analyse the potential reasons why those attempts to develop a treatment for early Alzheimer's disease failed. We compare the safety profiles of the different antibodies and highlight cautionary measures for their routine clinical use. Last, we discuss the role of blood-based biomarkers in transforming the clinical care pathway to facilitate the uptake of antibody treatments, proposing an integrated case-finding and treatment model crossing the different healthcare sectors.

Taken together, a real breakthrough may have been achieved by proving that amyloid-β reduction results in clinical benefits, rather than just biomarker changes. At the same time, routine use of the new generation of drugs will show if statistical efficacy translates into clinically meaningful change. This may just be the beginning of a new era of Alzheimer's disease drug development.

1 Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich 80336, Germany
2 German Center for Neurodegenerative Diseases (DZNE) Munich, Munich 81377, Germany
3 Munich Cluster for Systems Neurology (SyNergy), Munich 81377, Germany
4 Ageing Epidemiology (AGE) Research Unit, School of Public Health, Imperial College London, London W6 8RP, UK
5 Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Sheffield S10 2HQ, UK
6 Department of Psychiatry and Psychotherapy, University of Cologne, Cologne 50937, Germany
7 German Center for Neurodegenerative Diseases (DZNE) Bonn, Bonn 53127, Germany
8 Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, 50937 Cologne, Germany
9 Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar, Technical University of Munich, School of Medicine, Munich 81675, Germany
10 Department of Neurology, University Hospital, LMU Munich, Munich 81377, Germany
11 Department of Neurology, University Medicine Greifswald, Greifswald 17475, Germany
12 Department of Psychiatry and Psychotherapy, Charité, Campus Benjamin Franklin, Berlin 12203, Germany
13 German Center for Neurodegenerative Diseases (DZNE) Berlin, Berlin 10117, Germany
14 Department of Geriatric Psychiatry, Central Institute of Mental Health, Mannheim 68159, Germany

Correspondence to: Prof. Dr Robert Perneczky, MBA
Division of Mental Health in Older Adults and
Alzheimer Therapy and Research Center
Department of Psychiatry and Psychotherapy
University Hospital, LMU Munich Nussbaumstr 7

Received December 11, 2022. Revised December 23, 2022. Accepted January 04, 2023. Advance access publication January 19, 2023

Munich 80336, Germany
E-mail: robert.perneczky@med.uni-muenchen.de

Keywords: mild cognitive impairment and dementia; anti-amyloid immunization; treatment of cognitive decline; disease progression; monoclonal antibodies; fluid and imaging biomarkers

Introduction

Longer life expectancies are a major achievement of modern societies, but due to the ageing global population the number of dementia sufferers is increasing rapidly, currently affecting around 55 million individuals worldwide, estimated to increase to 132 million by 2050.[1] Dementia has a tremendous negative impact on the affected families' lives and budgets for social and healthcare, with estimated global costs of US$1 trillion in 2018, expected to double by 2030. Alzheimer's disease, the most prevalent cause of dementia, is an incurable, progressive neurodegenerative disorder, severely limiting the quality of life of those affected and their care partners. The presymptomatic stage can last decades, followed by an increasing decline in cognitive performance [mild cognitive impairment (MCI) stage] with subsequent progressive impairment of everyday function, changes of behaviour and complete dependency of others (dementia stage).

New disease-modifying therapies (DMT) promise a step change in dementia care and prevention. At present, monoclonal antibodies (mAbs) targeting amyloid-β (Aβ) are the most prevalent drugs in phase III trials,[2] with robust evidence on their engagement of the biological target in humans.[3–6] However, clinical efficacy is less consistent across different agents, and the overall trial evidence so far indicated that successful Aβ clearance in early Alzheimer's disease has at best very small effects on cognitive decline.[7] Our present update aims to elucidate the key reasons for those inconsistencies. To showcase the challenges with developing DMTs for Alzheimer's disease, we start with an analysis of the three most recent anti-Aβ mAbs with completed phase III trials (Table 1). We provide reasons why results of meta-analyses of the previous trials[7] are less relevant in the appreciation of the new lecanemab data,[8] including differences in drug dose, cohort characteristics, mAb specificity and adverse events.

Aducanumab: the first approval for two decades

Aducanumab, a human IgG1 mAb targeting amino acids 3–7 of the Aβ peptide, is specific for Aβ plaques[9] and on 7 June 2021, the US Food and Drug Administration (FDA) approved aducanumab for the treatment of Alzheimer's disease.[10] Initially, the FDA had formally accepted a regular approval procedure for review in August 2020. In November the same year, the FDA's independent advisory committee voted against the approval, stating that the data presented in the available studies did not support the drug's clinical efficacy sufficiently. Despite those reservations, the FDA subsequently concluded that the filing met the criteria for an accelerated approval process, in which confirmatory proof of clinical efficacy is not mandatory, and approval is possible based on surrogate marker data only. Since the evidence for reduction of Aβ deposits linked to better outcome was considered reasonably robust, the FDA considered aducanumab to meet this criterion and therefore granted accelerated approval, with the requirement of a confirmatory phase IV trial.

Aducanumab is the first DMT to be approved for Alzheimer's disease. A first small phase I study investigating the safety of aducanumab already showed significant Aβ reduction, and clinical data suggested possible cognitive benefits.[11] Therefore, the FDA allowed the usual phase II studies to be skipped and two phase III studies with about 1640 participants each to be conducted. These studies were stopped prematurely in March 2019 based on an interim evaluation in December 2018, since the likelihood of both trials meeting the primary end point was considered low.[12] As a consequence, 37% of participants were unable to complete the 78-week study period. In October 2019, the developer announced that upon re-evaluation of all available data, the results supported the clinical efficacy of the drug. This new conclusion was based on new data from an additional 318 participants collected before the discontinuation of the studies, but after the cut-off date for the interim evaluation. In one of the two studies, the highest aducanumab dose significantly slowed clinical deterioration on the Clinical Dementia Rating Scale-sum of the boxes (CDR-SB)[13,14] by 22%. A lower dose in this study and both doses in the second study showed no statistically significant superiority over placebo. Only a *post hoc* subgroup analysis of the highest cumulative dose in the negative second study provided evidence of efficacy.[15] As with other mAbs directed against Aβ, side effects also occurred during treatment with aducanumab. Of particular importance were amyloid-related imaging abnormalities with oedema (ARIA-E) and/or microhaemorrhages (ARIA-H) on brain MRI scans,[16] with an incidence of 35% and 36% in the two phase III studies, and 25% of affected participants experiencing symptoms, particularly in carriers of the *APOE* ε4 allele.[17]

While the primary aim of the phase III studies was to provide evidence for the clinical efficacy of aducanumab, the approval now granted is based on proof of meeting the surrogate biomarker end point of reducing Aβ plaques on PET. This accelerated approval route chosen by the FDA for aducanumab is intended for drugs targeting serious diseases, expected to have a significant added value over the available therapy, even if there is residual uncertainty about the ultimate clinical benefit.[18] There must be substantial evidence for efficacy on a surrogate end point reflecting the underlying disease pathology, with no requirement for demonstration of any clinical benefit. While biomarker evidence was sufficient for approval by FDA, the European Medicines Agency was unlikely to follow the US decision, and the developer therefore withdrew the marketing authorization application; approval for the marketing of aducanumab will not be granted in the EU.[19]

Lecanemab: the first disease-modifying drug with consistent evidence for clinical efficacy

Lecanemab (BAN2401) is the humanized version of murine mAb158, raised against Aβ protofibrils harbouring the mid-Aβ-domain arctic-APP mutation.[20,21] *In vitro*, Aβ monomers rapidly form protofibrils, and therefore some researchers view them as particularly important for driving downstream pathological changes, potentially hinting at their superior therapeutic properties. On 27 September 2022, results were announced from CLARITY AD, a large worldwide clinical trial with 1795 participants with early Alzheimer's disease, showing that lecanemab had achieved its

Table 1 Defining trial characteristics of the three most recent mAbs directed against Aβ tested in phase III trials

Monoclonal antibody	Trial name	Number of participants	Dosing length (weeks)	Dose per month (mg)[a]	CDR-SB change[b]	PET centiloid baseline visit[c]	PET centiloid final visit[c]	PET centiloid change[d]
Aducanumab	EMERGE	1643	78	1500	−0.39 (−22%)	85	25	−60
	ENGAGE	1653	78	1500	+0.03 (+2%)	91	37	−54
Lecanemab	CLARITY-AD	1906	78	1500	−0.45 (−27%)	78	23	−55
Gantenerumab	GRADUATE 1	984	116	1020	−0.31 (−8%)	92	34	−58
	GRADUATE 2	975	116	1020	−0.19 (−6%)	98	51	−47

ClinicalTrials.gov and sponsor data.
[a]Average cumulative dose in mg/month.
[b]Clinical Dementia Rating-sum of the boxes (CDR-SB) change between baseline and last visit compared to placebo.
[c]Aβ PET centiloid measurement in the lecanemab treatment group.
[d]Aβ PET change compared to baseline centiloid measurement.

primary end point, a statistically significant slowdown of clinical disease progression on the CDR-SB.[22] In this phase III trial the treatment group received 10 mg/kg lecanemab intravenously every 2 weeks, with participants receiving either placebo or lecanemab in a 1:1 ratio. The inclusion criteria allowed patients to enter the study with a wider range of concomitant diseases and co-medications compared to the other anti-Aβ mAb trials. Over the 18-month study period, both groups deteriorated on the CDR-SB and on other secondary clinical end points, as expected in Alzheimer's disease. However, clinical deterioration in the lecanemab group was 27% slower compared to placebo after 18 months, resulting in a statistically highly significant difference ($P < 0.0001$).[8] In the intent-to-treat population, this translated to a treatment difference in CDR-SB change of −0.45. The CDR-SB score is obtained by summing each of the CDR domain box scores, with scores ranging from 0 to 18 (higher scores indicating more severe impairment); participants in the lecanemab trial, however, had scores between 0.5 and 3. A brief discussion on defining clinical meaningfulness is provided in the Supplementary material. All secondary end points were also met with statistically significant results compared to placebo ($P < 0.01$), including global cognition (−1.44 change on the ADAS-cog14; range, 0 to 90, with higher scores indicating greater impairment)[23] and activities of daily living (+2.0 change on the ADCS-MCI-ADL; range, 0 to 53, with lower scores indicating greater impairment).[24,25] Importantly, lecanemab also showed superior efficacy on measures of quality of life and caregiver burden compared to placebo.

Lowering Aβ on PET, the main biological secondary end point measured in a subset of 698 patients, also favoured lecanemab over placebo ($P < 0.01$). After 18 months, the mean Aβ level in the lecanemab group was reduced by 55.48 centiloids compared to a reduction of 3.64 centiloids in the placebo group, resulting in an Aβ level below the threshold for positivity.[26] These findings support a positive relationships between the magnitude of Aβ lowering and the degree of clinical benefit, as already suggested for other mAbs (Fig. 1), and underline the importance of lowering Aβ level below the positivity threshold. All biomarkers of tau pathology and neurodegeneration in CSF and in plasma also favoured lecanemab over placebo, except for neurofilament light chain, strongly supporting the assumption of disease modification. On 6 January 2023 the FDA approved lecanemab under the accelerated approval pathway as the second drug ever for the treatment of Alzheimer's disease.[27]

Similar to the treatment with other mAbs directed against Aβ, side effects also occurred during treatment with lecanemab. Of particular importance were ARIA-E and ARIA-H, with an overall incidence of ARIA-E of 12.6% in the lecanemab group and 1.7% in the placebo group, whereas the incidence of symptomatic ARIA-E was 2.8% in the lecanemab group, and no symptomatic cases were detected in the placebo group. The ARIA-H rate was 17.3% in the lecanemab group and 8.7% in the placebo group, with an incidence of symptomatic ARIA-H of 0.7% in the lecanemab group compared with 0.2% in the placebo group. For isolated ARIA-H (i.e. cases with no ARIA-E at the same time), there was no imbalance between lecanemab (8.8%) and placebo (7.6%). Overall, ARIA under lecanemab treatment appear to be less frequent compared to other mAbs, contributing to a more favourable benefit-risk ratio, but direct comparisons may be misleading due to differences in study design, patient characteristics and mAb properties. Three reported cases of fatal brain haemorrhage may be associated with lecanemab and concomitant anticoagulant treatment,[29,30] suggesting that patients on anticoagulants may not be eligible for anti-Aβ mAb treatment until further safety data are available.[31] ARIA may lead to functional unblinding of study participants; therefore, different raters assessed clinical efficacy and safety, and efficacy raters remained blinded to ARIA assessments. Furthermore, removing data from participants who developed ARIA-E from the analyses did not change the efficacy results, suggesting the positive findings were not due to inadvertent unblinding of participants.[8] However, no similar analyses were performed for more common infusion-related reactions (26.4% for lecanemab versus 7.4% for placebo), raising the possibility of bias.

Gantenerumab: an unexpected failure?

Gantenerumab has a conformational epitope targeting both N-terminal and mid-domain Aβ-epitopes in plaques, with only limited binding of soluble Aβ.[32] Previously, subcutaneous application of gantenerumab was tested in two phase III trials (SCarlet RoAd and Marguerite RoAd) in patients with Aβ pathology confirmed by CSF randomized to either 105 or 225 mg/month.[33] However, the study was terminated prematurely due to futility after 50% of participants had reached the 104-week time point. In the high-dose group, compared to baseline only a 4.8% reduction of Aβ on PET was observed. Subsequently, both trials were converted to open label extension studies evaluating safety and efficacy of higher doses of gantenerumab up to 1200 mg/month subcutaneously. Of 81 patients enrolled, 40 met criteria for high-dose analysis, showing three times the PET Aβ change observed at the 225 mg dose, with one-third of participants showing Aβ levels below the cut-off point for positivity at Week 52.[5] Following those promising results, two new phase III trials in patients with early Alzheimer's disease were launched with gantenerumab doses titrated up to 1020 mg/month subcutaneously.

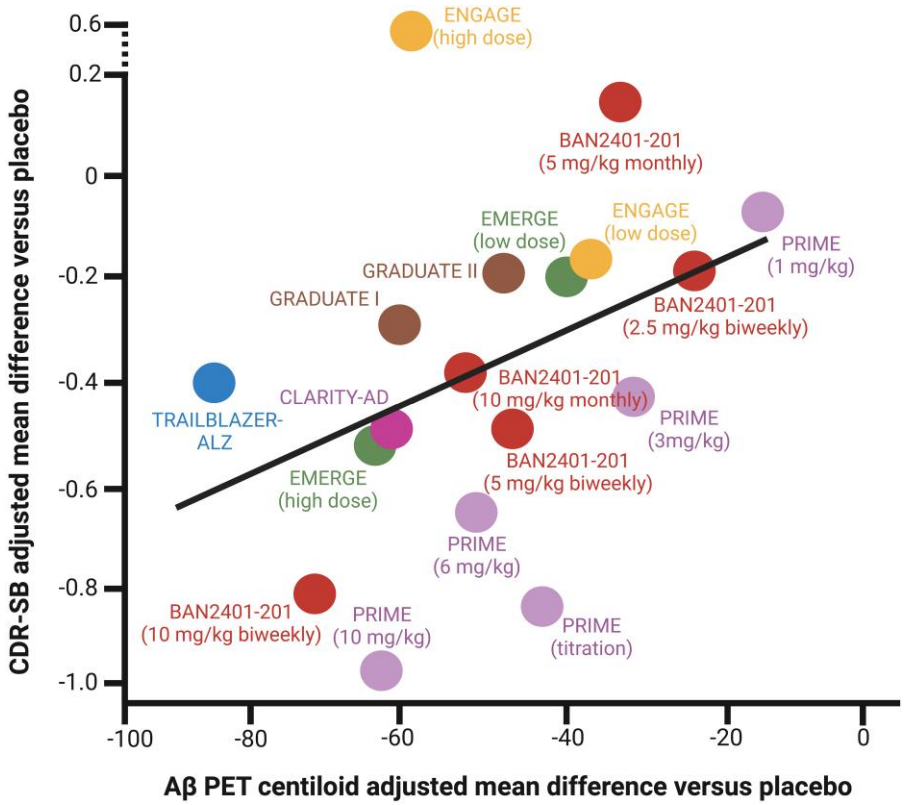

Figure 1 Association between Aβ plaque burden reduction (in PET centiloids) and preserving of clinical function (on CDR-SB) across different antibody trials. Illustrative depiction of the Aβ plaque reducing effect of different mAbs in relation to their clinical efficacy across phase I, phase II and phase III clinical trials (including trials with early termination). Multiple dose levels for select drug candidates are presented. The trend line across the different trials indicates the approximate relationship. There appears to be an association between Aβ plaque reduction and preservation of clinical function, which however is not entirely consistent across the different trials. Lowering PET centiloids below the positivity threshold for Aβ may be a more important indicator of clinical efficacy. Moreover, soluble Aβ species may be more relevant than plaques measured by PET. Source: FDA[28] and developer data.

On 13 November 2022, the results of the GRADUATE 1 and 2 trials were announced, indicating that gantenerumab failed to meet the primary end point of a 20% reduction of clinical disease progression. The drug had been under development since 2010 in nine clinical trials with 4135 patients with early Alzheimer's disease, and only slowed clinical decline by 8–9% in the two pivotal phase III trials after 27 months treatment on the primary end point CDR-SB (treatment difference in CDR-SB change of 0.24–0.34); secondary end points consistently showed a numerical slowing of decline by 9–12%. Biomarkers of tau pathology and neurodegeneration in CSF favoured gantenerumab over placebo underscoring the ability of disease modification also for this antibody. Aβ reduction of 21.1–24.1 centiloids at Week 54 and 46.8–57.6 at Week 116 was lower than anticipated. Interestingly, the placebo groups deteriorated by 3.2–3.9 points on the CDR-SB, about twice as much as the placebo groups in the aducanumab and lecanemab studies, possible due to required substantial episodic memory impairment at inclusion. Also, the frequency of ARIA under gantenerumab was higher than in the lecanemab, but lower than in the aducanumab, phase III trials (overall ARIA-E: 23.9–25.8% and 1.7.–3.8 in gantenerumab and placebo, respectively, symptomatic ARIA-E: 4.8–5.2% and 0.0–0.4%; ARIA-H: 22.0–23.7% and 12.2.–12.4%), and discrepant to the relative lack of Aβ removal on PET.

Reasons for differences in efficacy of select antibodies

Differences in clinical efficacy between the different mAbs directed against Aβ suggest that biological properties and trial design characteristics may play important roles, even though all considered agents target the Aβ protein. Taking gantenerumab as an example of a negative but well executed clinical trial to develop a DMT for Alzheimer's disease, the following explanations are plausible:

(i) The dose (or amount of antibody) of gantenerumab was too low to meet the primary end point. It is known that only a small fraction of a systemically administered IgG antibody arrives in the patients' brains,[34] a hypothesis supported by the lower than anticipated reduction of fibrillar Aβ on PET in the first gantenerumab phase III trials. Hence, the antibody dose in the GRADUATE trials was increased substantially after the initial studies, accepting a higher incidence of ARIA. However, the amount of antibody applied in the gantenerumab (1020 mg/month) and aducanumab trials (on average 750 mg/month) was still lower compared to lecanemab (on average 1500 mg/month). The subcutaneous administration of gantenerumab may have further led to lower peak concentrations of circulating antibodies compared with the intravenous application of lecanemab and aducanumab.

(ii) Patients in the gantenerumab trials may on average had a more advanced stage of disease, leading to a more rapid clinical decline: this difference in key cohort characteristics or other aspects of the inclusion and exclusion criteria may have impacted negatively on treatment-placebo difference on the study end points. In patients with more advanced disease, the ability of mAbs to show clinical efficacy may be limited. The cohort of patients treated with lecanemab had a higher proportion of multimorbidity than those in the gantenerumab or aducanumab trials, but differences between highly selected trial cohorts and the general population are likely even more pronounced[35] and it remains to be seen how those difference will affect the efficacy of any new approved DMT.

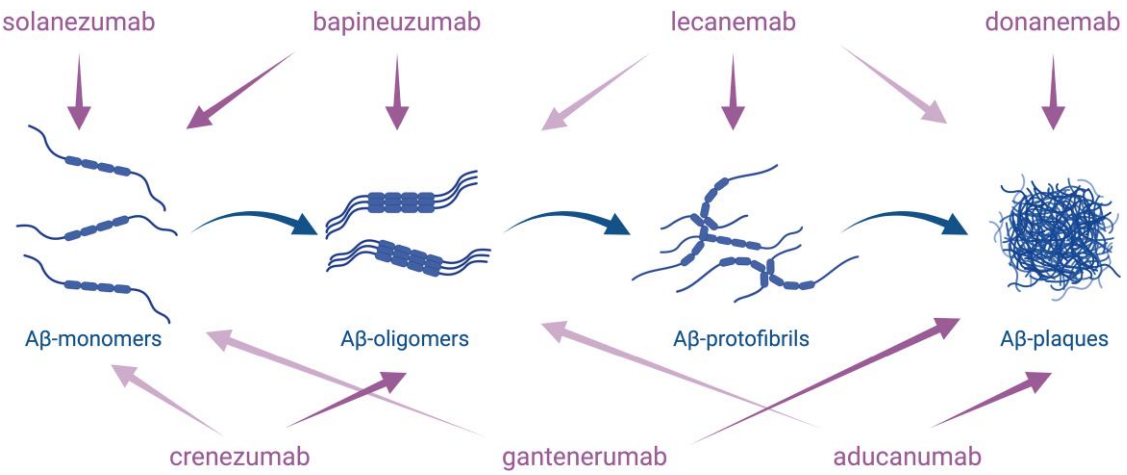

Figure 2 Schematic comparison of different antibodies directed against different aggregation states of Aβ. Source: Developer data

(iii) Gantenerumab may lack specificity for the assumed optimal treatment target: in contrast to lecanemab, directed specifically against Aβ fibrils and protofibrils, gantenerumab mostly targets Aβ deposits (i.e. plaques) and to some extent soluble Aβ monomers. It is not entirely clear how important this difference in the specificity of the antibody is; however, all first generation mAbs (solanezumab, crenezumab and bapineuzumab) were directed against Aβ monomers, and they all failed to show significant clinical efficacy, supporting the hypothesis that Aβ (proto)fibrils are a promising treatment target (Fig. 2).

(iv) For a full appreciation of the benefit-risk ratio, safety and tolerability aspects must be considered in detail. Infusion-related reactions occurred in 7.4% of patients under placebo and in 26.4% under lecanemab. For aducanemab, similar data were not reported.[15] ARIA are typical substance-specific adverse events of anti-Aβ antibodies, observed on brain MRI. Hence, patients unable to undergo MRI cannot be treated safely with anti-Aβ mAbs. The biological mechanisms of ARIA have yet to be elucidated, but they may be caused by increased cerebrovascular permeability owing to increased clearance of Aβ neuritic plaques and associated saturation of perivascular drainage, paired with direct mAb interaction with deposited vascular Aβ and weakening of the vessel wall. The first reports of cerebral vasogenic oedema and microhaemorrhages associated with anti-Aβ mAb therapy were observed following bapineuzumab treatment in a phase II multiple ascending dose trial.[36] ARIA were also observed in clinical trials of several other anti-Aβ mAb therapies, including gantenerumab, donanemab, lecanemab and aducanumab.[37] Most cases of ARIA are transient. The lower overall incidence of ARIA under lecanemab as compared to aducanumab appears clinically important, but the reasons for those differences are yet to be found. Clinical vigilance for ARIA should be highest after treatment initiation, and routine surveillance MRIs need to be supplemented with *ad hoc* scans in patients with new-onset symptoms indicative of ARIA. Approximately 25% of ARIA are symptomatic, potentially leading to a considerable load of MRI monitoring.[16] In patients with ARIA, the radiographic and clinical findings must be carefully assessed when deciding about further dosing. Weakening of the vessel wall as the common hypothesized event for ARIA may interact unfavourably with anticoagulants.[38]

Preparing healthcare systems for anti-Aβ antibody uptake

The World Health Organization's 2017 dementia plan sets priorities for global action across seven areas, including improved dementia diagnosis, treatment and care.[39] However, healthcare systems are not prepared to detect cognitive decline effectively, to diagnose early-stage disease accurately, and to identify the best intervention or deliver DMT in the future.[40] While knowledge about dementia and its causes is increasing rapidly, healthcare systems remain ill-equipped to detect cognitive decline in the early stages of neurodegenerative diseases such as Alzheimer's disease. Improving the identification of early changes in the population is a prerequisite for dementia prevention and providing future disease-modifying treatments for individuals most likely to benefit. MCI may indicate early Alzheimer's disease, and in conjunction with an Alzheimer's disease-typical biomarker profile, the risk of further cognitive decline increases significantly.[41] Offering cognitive evaluations to individuals with MCI may therefore open a window of opportunity for early intervention. Community and primary care medicine-based efforts are needed to increase the number of accurately identified subjects with early Alzheimer's disease, who will initially be eligible for treatment with the new DMTs. At present, no effective system for the identification of early symptomatic Alzheimer's disease cases is in place anywhere in the world, precluding efforts to detect Alzheimer's disease in large parts of the population. Supplementing the assessment of cognitive complaints by self-administered cognitive tests and blood-based Alzheimer's disease biomarkers may offer a feasible approach for effective and cost-efficient case finding programmes, potentially in newly established brain health clinics, preparing the healthcare systems for the targeted delivery of new DMTs.[42] However, the added value of the different strategies has yet to be determined.[43]

Similar to CSF[44] and PET[45] markers of Alzheimer's disease, appropriate use scenarios for blood-based biomarkers (BBBM) must be developed to maximize patient benefit. According to the recent Alzheimer's Association guidelines,[46] only symptomatic individuals assessed in specialist centres should undergo BBBM testing as a supporting diagnostic tool to supplement detailed clinical assessments, never as a standalone test. Relevant cut-off points for abnormality and the impact of confounding conditions must be established before BBBM can be offered in routine care, and results should be confirmed whenever possible by PET/CSF. There is evidence that phosphorylated-tau in particular can identify Alzheimer's disease pathology and predict clinical worsening in MCI and differentiate Alzheimer's disease dementia from other neurodegenerative disorders in memory clinic populations.[47] A staged approach may be most appropriate, with negative BBBM results used to rule out individuals with a very low likelihood of Alzheimer's disease pathology, and only those with a positive result (and higher likelihood of underlying Alzheimer's disease) being referred for confirmatory CSF or PET. In an alternative scenario,

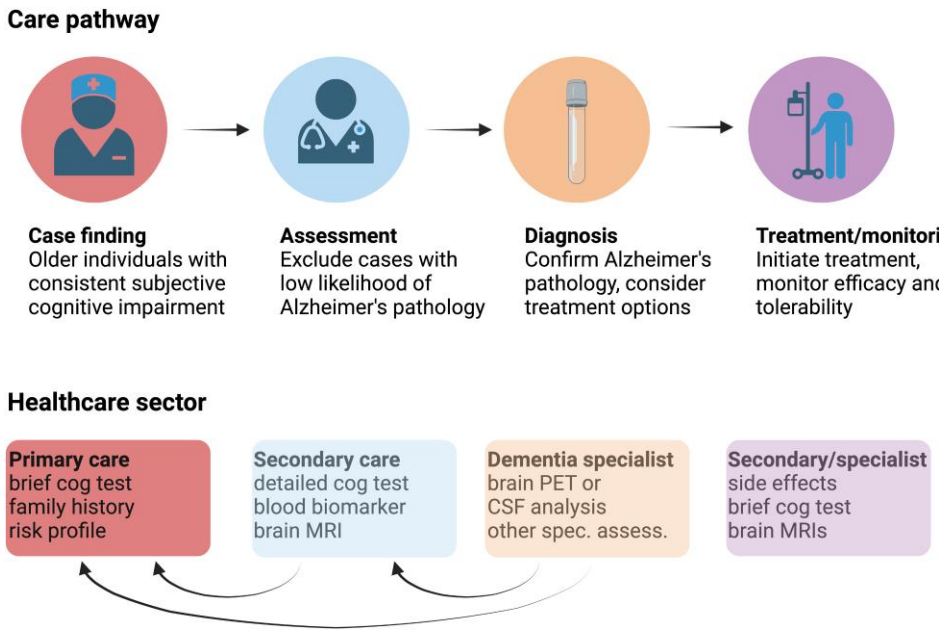

Figure 3 Proposed diagnostic pathway for early Alzheimer's disease case finding, diagnosis and treatment. Proposed model of a care pathway to identify older individuals with minor cognitive complaints/deficits in primary care, followed by an exclusion of subjects with very low likelihood of Alzheimer's disease pathology in secondary care (e.g. by using blood-based biomarkers) and subsequent diagnostic confirmation by a dementia specialist (e.g. by using PET and CSF markers) as well as initiation of DMT treatment after careful evaluation of potential risks and benefits, including monitoring of side effects. Individuals can also move backwards in this model if they do not meet criteria for progression to the next stage (e.g. negative blood-biomarker for Alzheimer's disease).

three risk groups could be identified, including low-risk for Alzheimer's disease individuals with no requirement for further assessments, intermediate-risk individuals referred for CSF or PET and high-risk individuals immediately eligible for DMT therapy after careful consideration of potential risks and benefits.

The high proportion of missed dementia diagnoses is a global problem, and particularly pronounced in low-resource regions.[48] Therefore, case finding in primary care must be improved urgently, but the evidence on performance of BBBM in identifying Alzheimer's disease in those settings is sparse. Findings from specialist clinics cannot be extrapolated to primary care since Alzheimer's disease prevalence is much lower and populations are more heterogeneous in terms of co-pathologies and co-morbidities compared to memory clinics. Routine use of BBBM to identify individuals most likely to benefit from DMTs is therefore a more distant hope.

Conclusion

Whether and to what extent the statistically significant clinical effects of a drug in a clinical trial translate to a significant benefit for individuals outside of the controlled study environment can ultimately only be determined under real-world conditions after the approval of a mAb directed against Aβ. Aducanumab is unlikely to provide the comprehensive data required due to the limited approval and coverage in the US, but other agents, including lecanemab, offer a more realistic option to gain valuable insights. Since the current generation of anti-Aβ mAbs will likely only retard disease progression, rather than stop neurodegeneration, further research into key Alzheimer's disease pathomechanisms is warranted. A combination of drugs targeting different biological mechanisms (e.g. Aβ, tau, inflammatory) may be most promising, including compounds with symptomatic effects. Having one component of such an approach now means that trials of drug combinations have a firm basis from which to start, potentially facilitating the development of effective combinations. With a DMT for Alzheimer's disease on the horizon, the healthcare systems globally will have to adapt to the changing environments, healthcare pathways have to evolve to allow for wider drug uptake and different key players must collaborate more closely, including primary, secondary and specialist care. Initially, DMT treatment should only occur in specialized centres such as brain health or memory clinics, experienced in Alzheimer's disease diagnosis and care, with access to advanced resources such as PET. Certification of those centres may help to set the appropriate standards, and the processes will vary by country. Restricting DMTs to specialist settings will not only ensure optimal care, but also allow clinicians to gain experience in effectively identifying patients who would benefit most and are at a lower risk of side effects, and to learn how to best initiate, evaluate and stop treatment (Fig. 3).

Funding

R.P. is supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy—ID 390857198), the Davos Alzheimer's Collaborative, the VERUM Foundation, the Robert-Vogel-Foundation, the German Center for Neurodegenerative Diseases (DZNE), the Sheffield National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) and the University of Cambridge—Ludwig-Maximilians-University Munich Strategic Partnership within the framework of the German Excellence Initiative and Excellence Strategy. L.F. is supported by the Hector II Foundation.

Competing interests

R.P. has received honoraria for advisory boards and speaker engagements from Roche, EISAI, Eli Lilly, Biogen, Janssen-Cilag, Astra Zeneca, Schwabe, Grifols, Novo Nordisk and Tabuk; and was principal investigator on the aducanumab phase-III trials. L.F. has received grants, consultancy fees or lecture honoraria from Biogen, Eisai, Grifols, Hummingbird, InfectoPharm, Janssen-Cilag, Merck Sharpe and Dohme, Neurimmune, Neuromodulation, Noselab, Novo Nordisk, Roche, TauRX, Schwabe, has served on Data and Safety Monitoring boards with Otsuka, Pharmatrophix, Forschungszentrum Jülich, Charité Berlin, Neuroscios and Vivoryon, was principal investigator on the lecanemab and gantenerumab phase-III trials and is a co-author on the publication of the lecanemab phase-III study data.[8] T.G. has received consulting fees from AbbVie, Alector, Anavex, Biogen, Eli Lilly, Functional Neuromodulation, Grifols, Iqvia, Noselab, Novo Nordisk, NuiCare, Orphanzyme, Roche Diagnostics, Roche Pharma, UCB and Vivoryon; lecture fees from Grifols, Medical Tribune, Novo Nordisk, Roche Pharma, and Schwabe; grants to his institution from Roche Diagnostics; and was principal investigator on the aducanumab, lecanemab and gantenerumab phase-III trials. F.J. has received honoraria for advisory boards and speaker engagements from AC Immune, Biogen, Danone/Nutricia, Eisai, GE Healthcare, Grifols, Janssen, Lilly, MSD, Roche and Novo Nordisk. J.L. reports speaker fees from Bayer Vital, Biogen and Roche, consulting fees from Axon Neuroscience and Biogen, author fees from Thieme medical publishers and W. Kohlhammer GmbH medical publishers. In addition, he reports compensation for serving as chief medical officer for MODAG GmbH, is beneficiary of the phantom share program of MODAG GmbH and is inventor in a patent 'Pharmaceutical Composition and Methods of Use' (EP 22 159 408.8) filed by MODAG GmbH. O.P. has received grants, consultancy fees or lecture honoraria from Biogen, Eisai, Grifols, Neurotransdata, Novo Nordisk, Prinnovation/Priavoid, Roche and Schwabe. He was principal investigator on the aducanumab, lecanemab and gantenerumab phase-III trials.

Supplementary material

Supplementary material is available at *Brain* online.

References

1. Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Prina M. World Alzheimer report—the global impact of dementia. 2015.
2. Cummings J, Lee G, Nahed P, *et al*. Alzheimer's disease drug development pipeline: 2022. *Alzheimers Dement (N Y)*. 2022;8:e12295.
3. 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;370:322-333.
4. Salloway S, Honigberg LA, Cho W, *et al*. Amyloid positron emission tomography and cerebrospinal fluid results from a crenezumab anti-amyloid-beta antibody double-blind, placebo-controlled, randomized phase II study in mild-to-moderate Alzheimer's disease (BLAZE). *Alzheimers Res Ther*. 2018;10:96.
5. Klein G, Delmar P, Voyle N, *et al*. Gantenerumab reduces amyloid-beta plaques in patients with prodromal to moderate Alzheimer's disease: A PET substudy interim analysis. *Alzheimers Res Ther*. 2019;11:101.
6. Lowe SL, Duggan Evans C, Shcherbinin S, *et al*. Donanemab (LY3002813) phase 1b study in Alzheimer's disease: Rapid and sustained reduction of brain amyloid measured by florbetapir F18 imaging. *J Prev Alzheimers Dis*. 2021;8:414-424.
7. Richard E, den Brok M, van Gool WA. Bayes Analysis supports null hypothesis of anti-amyloid beta therapy in Alzheimer's disease. *Alzheimers Dement*. 2021;17:1051-1055.
8. van Dyck CH, Swanson CJ, Aisen P, *et al*. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2022;388:9-21.
9. Arndt JW, Qian F, Smith BA, *et al*. Structural and kinetic basis for the selectivity of aducanumab for aggregated forms of amyloid-beta. *Sci Rep*. 2018;8:6412.
10. FDA Grants Accelerated Approval for Alzheimer's Drug. Published 7 June 2021. Accessed 10 December 2022. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug
11. Sevigny J, Chiao P, Bussiere T, *et al*. The antibody aducanumab reduces Abeta plaques in Alzheimer's disease. *Nature*. 2016;537:50-56.
12. Biogen and Eisai to Discontinue Phase 3 ENGAGE and EMERGE Trials of aducanumab in Alzheimer's Disease. Published 21 March 2019. Accessed 10 Dec 2022. https://investors.biogen.com/news-releases/news-release-details/biogen-and-eisai-discontinue-phase-3-engage-and-emerge-trials
13. Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology*. 1993;43:2412-2414.
14. McDougall F, Edgar C, Mertes M, *et al*. Psychometric properties of the Clinical Dementia Rating—sum of boxes and other cognitive and functional outcomes in a prodromal Alzheimer's disease population. *J Prev Alzheimers Dis*. 2021;8:151-160.
15. Haeberlein S B, 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.
16. Barakos J, Sperling R, Salloway S, *et al*. MR Imaging features of amyloid-related imaging abnormalities. *AJNR Am J Neuroradiol*. 2013;34:1958-1965.
17. 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.
18. Sachs RE, Donohue JM, Dusetzina SB. Accelerated approval—taking the FDA's concerns seriously. *N Engl J Med*. 2022;387:199-201.
19. European Medicines Agency. Aduhelm: Withdrawal of the Marketing Authorisation Application. Published 22 April 2022. Accessed 10 Dec 2022. https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/aduhelm
20. Nilsberth C, Westlind-Danielsson A, Eckman CB, *et al*. The 'Arctic' APP mutation (E693G) causes Alzheimer's disease by enhanced Abeta protofibril formation. *Nat Neurosci*. 2001;4:887-893.
21. Lord A, Gumucio A, Englund H, *et al*. An amyloid-beta protofibril-selective antibody prevents amyloid formation in a mouse model of Alzheimer's disease. *Neurobiol Dis*. 2009;36:425-434.
22. Lecanemab Confirmatory Phase 3 Clarity AD Study Met Primary Endpoint, Showing Highly Statistically Significant Reduction of Clinical Decline in Large Global Clinical Study of 1,795 Participants With Early Alzheimer's Disease. Published 28 September 2022. Accessed 10 December 2022. https://www.eisai.com/news/2022/news202271.html
23. Mohs RC, Knopman D, Petersen RC, *et al*. Development of cognitive instruments for use in clinical trials of antidementia drugs: Additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11(Suppl 2):S13-S21.
24. Perneczky R, Pohl C, Sorg C, *et al*. Complex activities of daily living in mild cognitive impairment: Conceptual and diagnostic issues. *Age Ageing*. 2006;35:240-245.

25. Perneczky R, Pohl C, Sorg C, *et al*. Impairment of activities of daily living requiring memory or complex reasoning as part of the MCI syndrome. *Int J Geriatr Psychiatry*. 2006;21:158-162.
26. Fleisher AS, Chen K, Liu X, *et al*. Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Arch Neurol*. 2011;68:1404-1411.
27. FDA Grants Accelerated Approval for Alzheimer's Disease Treatment. Published 6 January 2023. Accessed 31 January 2023. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment
28. Clinical Pharmacology and Biopharmaceutics Review(s). Center For Drug Evaluation and Research. 7 July 2020. Accessed 11 Dec 2022. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000ClinPharm_Redacted.pdf
29. Piller C. Second death linked to potential antibody treatment for Alzheimer's disease. *Science*. Published 27 November 2022. Accessed 31 January 2023. doi:10.1126/science.adf9701
30. Pillar C. Scientists tie third clinical trial death to experimental Alzheimer's drug. *Science*. Published 21 December 2022. Accessed 31 January 2023. doi:10.1126/science.adg4121
31. Pfeifer M, Boncristiano S, Bondolfi L, *et al*. Cerebral hemorrhage after passive anti-Abeta immunotherapy. *Science*. 2022;298:1379.
32. Bohrmann B, Baumann K, Benz J, *et al*. Gantenerumab: A novel human anti-Abeta antibody demonstrates sustained cerebral amyloid-beta binding and elicits cell-mediated removal of human amyloid-beta. *J Alzheimers Dis*. 2012;28:49-69.
33. Ostrowitzki S, Lasser RA, Dorflinger E, *et al*. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. *Alzheimers Res Ther*. 2017;9:95.
34. Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: Formulation and delivery strategies. *Nat Rev Drug Discov*. 2014;13:655-672.
35. Anderson TS, Ayanian JZ, Souza J, Landon BE. Representativeness of participants eligible to be enrolled in clinical trials of aducanumab for Alzheimer disease compared with medicare beneficiaries with Alzheimer disease and mild cognitive impairment. *JAMA*. 2021;326:1627-1629.
36. Salloway S, Sperling R, Gilman S, *et al*. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. *Neurology*. 2009;73:2061-2070.
37. 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;7:367-385.
38. Winer JR, Mander BA, Helfrich RF, *et al*. Sleep as a potential biomarker of tau and beta-amyloid burden in the human brain. *J Neurosci*. 2019;39:6315-6324.
39. World Health Organization. Global Action Plan on the Public Health Response to Dementia 2017–2025. Published 8 December 2017. Accessed 11 December 2022. https://www.who.int/publications/i/item/9789241513487
40. Hlavka JP, Mattke S, Liu JL. Assessing the preparedness of the health care system infrastructure in six European countries for an Alzheimer's treatment. *Rand Health Q*. 2019;8:2.
41. Mattsson N, Zetterberg H, Hansson O, *et al*. CSF Biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA*. 2009;302:385-393.
42. O'Donoghue MC, Raymont V, Fossey J, *et al*. The Oxford Brain Health Centre: Embedding dementia research in clinical practice. *Alzheimers Dement*. 2020;16(Suppl 8):e044907.
43. Mielke MM, Dage JL, Frank RD, *et al*. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28:1398-1405.
44. Simonsen AH, Herukka SK, Andreasen N, *et al*. Recommendations for CSF AD biomarkers in the diagnostic evaluation of dementia. *Alzheimers Dement*. 2017;13:274-284.
45. Johnson KA, Minoshima S, Bohnen NI, *et al*. Appropriate use criteria for amyloid PET: A report of the amyloid imaging task force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Alzheimers Dement*. 2013;9:e1-e16.
46. Hansson O, Edelmayer RM, Boxer AL, *et al*. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2022;18:2669-2686.
47. Palmqvist S, Janelidze S, Quiroz YT, *et al*. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA*. 2020;324:772-781.
48. Holm E, Jacobsen KK, de Lony TB, *et al*. Frequency of missed or delayed diagnosis in dementia is associated with neighborhood socioeconomic status. *Alzheimers Dement (N Y)*. 2022;8:e12271.