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Testing the Amyloid Cascade Hypothesis: Prevention Trials in Autosomal Dominant Alzheimer Disease

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Structured Abstract

Objective: The amyloid cascade hypothesis of Alzheimer disease (AD) has been increasingly challenged. Here we aim to refocus the amyloid cascade hypothesis on its original premise that the accumulation of amyloid β-peptide (Aβ) is the primary and earliest event in AD pathogenesis as based on current evidence, initiating several pathological events and ultimately leading to AD dementia.

Background: An ongoing debate about the validity of the amyloid cascade hypothesis for AD has been triggered by clinical trials with investigational disease-modifying drugs targeting Aβ that have not demonstrated consistent clinically meaningful benefits.

Updated Hypothesis: It is an open question if monotherapy targeting Aβ pathology could be markedly beneficial at a stage when the brain has been irreversibly damaged by a cascade of pathological changes. Interventions in cognitively unimpaired individuals at risk for dementia, during amyloid-only and pre-amyloid stages, are more appropriate for proving or refuting the amyloid hypothesis. Our updated hypothesis states that anti-Aβ investigational therapies are likely to be most efficacious when initiated in the preclinical (asymptomatic) stages of AD

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and specifically when the disease is driven primarily by amyloid pathology. Given the young age at symptom onset and the deterministic nature of the mutations, autosomal dominant AD (ADAD) mutation carriers represent the ideal population to evaluate the efficacy of putative disease-modifying Aβ therapies.

Major Challenges for the Hypothesis: Key challenges of the amyloid hypothesis include the recognition that disrupted Aβ homeostasis alone is insufficient to produce the AD pathophysiologic process, poor correlation of Aβ with cognitive impairment and inconclusive data regarding clinical efficacy of therapies targeting Aβ. Challenges of conducting ADAD research include the rarity of the disease and uncertainty of the generalizability of ADAD findings for the far more common "sporadic" late onset AD.

Linkage to Other Major Theories: The amyloid cascade hypothesis, modified here to pertain to the preclinical stage of AD, still needs to be integrated with the development and effects of tauopathy and other co-pathologies, including neuroinflammation, vascular insults, synucleinopathy, and many others.

Keywords

Alzheimer disease; autosomal dominant Alzheimer disease; amyloid hypothesis; preclinical; prevention; therapy

Objective

Autosomal dominant Alzheimer disease (ADAD) is an ideal model to examine the amyloid cascade hypothesis by implementing interventions with putative disease-modifying drugs prior to the symptomatic onset of AD. We intend to 1) reconsider the role of amyloid-β (Aβ) treatments in preclinical AD, when amyloid pathology dominates, with the goal of preserving brain function and slowing cognitive decline before other relevant co-pathologies enter the stage, thus serving as a direct test of the amyloid cascade hypothesis; and 2) use the results of prevention trials in ADAD to inform similar trials to prevent the far more common "sporadic" late onset AD (LOAD).

Background

Historical evolution

The amyloid cascade hypothesis of Alzheimer disease (AD), first published in 1991,[1,2] incorporated observations about the ubiquitous presence of amyloid plaques in the brains of persons who experienced AD dementia during life with the discovery of mutations within the *amyloid precursor protein (APP)* gene[3] that cause autosomal dominant AD (ADAD). These *APP* mutations and subsequent ADAD-causing mutations in the *presenilin-1 (PSEN1)*[4] and *presenilin-2 (PSEN2)*[5] genes were shown to alter the processing of the *APP* protein such that the cleavage products resulted in relatively greater amounts of amyloidogenic fragments of the amyloid-beta (Aβ) peptide. Hence, studies of ADAD provided a genetic framework to support the amyloid cascade hypothesis.[6] Further support came from the demonstration that *apolipoprotein E ε4 (APOE4)*, the major genetic risk factor for sporadic late-onset AD (LOAD), was less effective than the APOE2 and APOE3

alleles in clearing Aβ from the central nervous system.[7] Additionally, almost all adults with Down syndrome, who have increased lifelong accumulation of Aβ due to overexpression of the *APP* gene owing to trisomy 21, almost all have neuropathological AD by age 40 years.[8] Finally, the discovery that the A673T coding variant in the *APP* gene reduces the generation of amyloidogenic Aβ peptides and robustly protects against LOAD[9] strongly supports the key tenet of the amyloid cascade hypothesis: Aβ aggregation and deposition as amyloid plaques in the brain parenchyma are the initiating events that culminate in AD dementia. In addition to these arguments, a recent report of a *PSEN1* mutation carrier, found to be also homozygote carrier for the *APOE3* Christchurch mutation, who did not develop clinical dementia in line with a minimal tau PET signal despite having substantial amyloid pathology, highlights the importance of studying genetic variants that may protect the brain from Aβ downstream neurodegenerative effects [10].

However, the amyloid cascade hypothesis has been increasingly challenged, both in the scientific literature[11] and in the press.[12] The arguments against the hypothesis are well-supported and can be summarized as follows: 1) disrupted Aβ homeostasis is a necessary but insufficient factor for the development of AD; 2) many of the pathological processes in AD that are thought to occur “downstream” of the parenchymal deposition of Aβ correlate better with symptomatic AD than does Aβ load, and some are proposed to themselves initiate the AD cascade[13]; and 3) to date, no investigational drug for AD, the majority of which have targeted Aβ, has clearly demonstrated efficacy in a phase 3 trial. The long track record of failed clinical trials in particular has prompted consideration of alternatives to the amyloid cascade hypothesis. However, more recently several development programs have been able to deliver either mixed results in phase III trials such as Aducanumab (EMERGE and ENGAGE) or indications of efficacy in early stage trials such as Donanemab and Lecanemab [14,15].

In this Theoretical Article, we contend that the amyloid cascade hypothesis remains compatible with the either mixed or disappointing results from late stage clinical trials with anti-Aβ therapies. In doing so, we slightly constrain the hypothesis to reflect that it best pertains to the preclinical (asymptomatic) stage of AD, prior to symptomatic onset. It has long been recognized that symptomatic AD (encompassing both mild cognitive impairment due to AD and AD dementia) develops only after the Alzheimer pathophysiologic process produces sufficient synaptic and neuronal damage to disrupt normal memory and other cognitive functions.[16] Once initiated, this synaptic and neuronal loss is both continuous and irreversible, and is expressed clinically by progressive cognitive and functional deterioration – the AD dementia syndrome. Many failed or not clearly successful clinical trials of anti-Aβ drugs, as well as trials with drugs targeting other potential mechanisms (e.g., inflammation, insulin resistance, and mitochondrial dysfunction) in the AD pathophysiologic cascade all enrolled participants with symptomatic AD, some in advanced or mixed stages. The lack of definite evidence of marked therapeutic benefit is understandable as none of the experimental agents restore damaged or lost neurons. The more recent trials which led to some signs of efficacy share that they require rigorous biomarker defined AD in early clinical stages as inclusion criterion and that some datasets contain hints towards an additional effect on tau pathology (see below).

Various scenarios have been proposed for the role of Aβ in initiating downstream pathophysiological processes, including tauopathy, that produce synaptic and neuronal loss and ultimately culminate in symptomatic AD[17]. The **Aβ threshold** scenario suggests that parenchymal Aβ deposition already has occurred but is not yet to the level that the full AD pathophysiology, including neuroinflammation and tau pathology, has been activated. In this scenario, the administration of anti-Aβ therapies prior to reaching the threshold for activation may arrest subsequent development of AD pathophysiology and thus prevent or delay the onset of symptomatic AD. This approach is evaluated with secondary prevention trials, where cognitively normal trial participants already manifest cerebral Aβ deposition as ascertained by positron emission tomography (PET) using radioligands for Aβ or by lowered Aβ concentrations in the cerebrospinal fluid (CSF). In the **Aβ trigger** scenario, the full Alzheimer disease process commences with the initial Aβ pathology and thus requires that anti-Aβ therapies be administered prior to *any* pathology if they are to be maximally effective. This scenario requires a primary prevention clinical trial design, where cognitively normal individuals without evidence of Aβ deposition are treated with the goal to avert the development of such pathology. The announcement of results from 2 identical phase 3 trials of aducanumab, suggesting a clinical benefit of this compound in one of this two studies, the small but positive effects observed with solanezumab[18], and the recently reported positive effect of donanemab on a composite measure of cognition and function may provide support for the Aβ threshold scenario. The aducanumab, solanezumab and donanemab[14] trials in sporadic AD together with the unpublished results of the BAN2401/lecanemab trials were the first larger studies that stipulated a positive Aβ status and treated AD patients in only early symptomatic stages [15]. Therefore, trials in ADAD may be promising as the nature of the disease allows for selection of even earlier Aβ positive asymptomatic disease stages. The aducanumab, solanezumab, lecanemab and donanemab data in sporadic AD raise the question about a clinically significant effect size. The available data for aducanumab, donanemab and lecanemab suggest that all these treatments led to a slowing in disease progression by approximately 10-30% in early symptomatic AD patients, which might be suggestive of a class effect. In these patients the downstream tau process is already on-going and several clinical trials of anti-Aβ agents have evinced changes in CSF tau and phosphorylated tau (aducanumbab, lecanemab, bapineuzumab [19,20]). Early data suggest that further spread of tau pathology might be slowed down by donanemab [14]. In this context, the observed clinical effects are in line with the good clinical pathological correlation of tau pathology in AD. The emerging image of these effects will be substantially clearer once results from ongoing pivotal trials of several Aβ plaque-reducing monoclonal antibody therapies (gantenerumab, lecanemab and donanemab) which are expected within the next 1-2 years, will be available.

ADAD provides the opportunity to intervene early in the disease process before downstream pathologies initiate and therefore treatment may result in larger effect sizes and ultimately proof the amyloid hypothesis.

Rationale

Experimental therapies targeting Aβ have demonstrated effects on biomarkers but to date no definite clinical and cognitive benefits have been reported from phase III efficacy studies

in symptomatic AD. This suggests that Aβ is not the main driver of the clinical disease progression in symptomatic disease stages. The clinically silent preclinical phase of AD may last two decades or longer before symptomatic AD appears [21-24]. This long asymptomatic stage of the illness that has been well-characterized by various cross-sectional [21,22] and longitudinal[23,24] studies provides the opportunity to intervene with anti-Alzheimer therapies with the hope that the onset of symptomatic AD can be delayed or even prevented.

Studies of the anti-Aβ antibodies gantenerumab and solanezumab did not demonstrate a clinical treatment benefit as assessed by a multivariate cognitive scale in the presymptomatic and early symptomatic disease phases of ADAD [25]. However, the asymptomatic groups did not decline and the trial was not powered to detect clinical effects of late high-dose titration. The strong biomarker effects on non-Aβ pathologies associated with Aβ-plaque reduction by gantenerumab in the DIAN-TU-001 study supports the need for early Aβ interventions and provides important information for planning future prevention studies in this population.

This Theoretical Article posits that the amyloid cascade hypothesis, when viewed in context of preclinical AD, still provides a compelling rationale for secondary and primary prevention trials in individuals from ADAD families using anti-Aβ and other investigational drugs in a biomarker-defined window of opportunity prior to symptomatic onset. The Alzheimer's Prevention Initiative (API) [26] and the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU)[27] provide frameworks for such trials. As to date, one open label extension, and one amyloid secondary prevention trial are in progress and more are being planned (table 1), as are primary prevention trials. The results of these trials will be the ultimate test of the amyloid cascade hypothesis of preclinical AD.

Updated hypothesis

Early observational data: The search for biomarkers of preclinical AD

AD biomarkers play growing roles in diagnosis, disease staging, and drug development, and may have predictive or prognostic properties. Established AD-related biomarkers to date include "downstream" markers of neuronal dysfunction or disintegration such as glucose metabolism measured by fluorodeoxyglucose positron emission tomography (FDG-PET) and volumetric magnetic resonance imaging (MRI) measurements of brain atrophy. Molecular markers include PET measurements of fibrillar Aβ, and cerebrospinal fluid (CSF) concentrations of amyloid ($A\beta_{1-42}$), tau, and phosphorylated tau.[23,24] Compared to brain atrophy and hypometabolism, molecular biomarkers have the best AD specificity. CSF biomarkers have shown prognostic value in terms of predicting progression from the preclinical to clinical stages of AD.[28] In lieu of studying a large group or waiting long periods of time to assess cognitive endpoints of AD intervention trials, research with ADAD provides a more efficient way for longitudinal validation of biomarkers from the preclinical phase through symptomatic disease.[29]

Biomarker changes for ADAD in many but not all cases are similar to those seen in LOAD (table 2). Cross-sectional and longitudinal studies from DIAN and API have shown that levels of $A\beta_{1-42}$ in CSF start to decline approximately 20-25 years before estimated age at onset of clinical symptoms. Soluble Aβ changes are followed by brain Aβ deposition at

16-25 years prior to estimated year of symptom onset (EYO), hypometabolism at −17 to −10 EYO, hippocampal atrophy at −15 to −1 EYO, increased CSF total tau and phosphorylated tau at −21 to 1 EYO, tau pathology as measured by PET imaging at −6 to 0 EYO and clinical onset near 0 EYO (figure A).[21-24,30-32] Plasma $A\beta_{1-42}$ levels are consistently elevated from −15 EYO on[21].

Tau levels, as measured by PET imaging, are more strongly associated with cognitive decline than brain Aβ.[30,31,33] The above-mentioned biomarker studies support the hypothesis that amyloid pathology precedes and likely triggers neurodegeneration and cognitive decline in ADAD, consistent with data from older individuals at high risk for LOAD.[34]

Limitations of AD biomarkers include the fact that Aβ is not robustly linked to clinical presentation. However, recent data show a correlation of the duration of Aβ-positivity with the risk for cognitive decline and change in other AD-related biomarkers. [35] Downstream biomarkers such as brain atrophy do not occur until very late in the preclinical stage.[23,24] Therefore, it will likely be necessary to employ novel measures of the AD pathological process (e.g. blood based assays [36]) that are sensitive, specific and reproducible biomarkers for detection of AD-related neuropathological changes over time. For example, blood neurofilament light (NfL) chain dynamics is a promising biomarker that predicts disease progression and neurodegeneration early in the preclinical stage of ADAD.[37] This would be important to improve the efficiency and probability of success of future prevention trials. Efforts are still needed to validate reliable, minimally invasive, and inexpensive methods for detection and monitoring of AD progression and estimation of therapeutic benefit.

Future experiments and validation studies

All key processes contributing to AD pathogenesis may be considered therapeutic targets for future interventional trials. The most prominent targets include Aβ- and tau- pathology, but also microglia activation [38] as well as other targets, such as synuclein-pathology[39], oxidative stress [40] or virus activation [41] may also play a role in future trials. All ADAD mutations converge mechanistically on an alteration in the processing of APP [42]. Available agents targeting Aβ were developed primarily using models based on ADAD mutations.[42] Insight in the time course of biomarkers allows prediction of biomarker defined disease stages in ADAD (figure A). Therefore, ADAD studies provide a unique opportunity to explore the efficacy of anti-Aβ treatments in biomarker-defined windows of opportunity, even before the onset of measurable Aβ-pathology and in a genetically determined, Aβ-only phase before the other co-pathologies of AD develop.[23,24]

Current ongoing and completed ADAD trials in the API and DIAN have used anti-Aβ immunotherapy, (table 1) which is designed to increase clearance of several different forms of Aβ. In the API ADAD trial (NCT1998841) mutation carriers from a single-mutation kindred are treated with Aβ immunotherapy (crenezumab) or placebo, respectively. Crenezumab is an antibody that shows a minimal fc-effector response and binds to the mid-domain of monomeric and aggregated forms of Aβ, with highest affinity for oligomers.[26] The DIAN-TU (NCT01760005) is a platform that recently completed two drug arms with two different Aβ immunotherapies: 1) Solanezumab, an antibody that binds to the mid-

domain of the Aβ peptide and targets soluble monomeric Aβ,[43] and 2) gantenerumab, an antibody against the N-terminal epitope of Aβ that binds its aggregated forms, including oligomers and fibrils.[43] Both DIAN-TU trial arms did not meet their primary endpoint, the change from baseline in the DIAN-TU Cognitive Composite. However, in this first-ever completed anti-Aβ trials in ADAD several factors limit the interpretation of clinical efficacy including the relatively small sample size, the combined analyses of asymptomatic and symptomatic individuals, the late initiation of high drug doses, and the little to no cognitive decline that was expected in asymptomatic participants. With respect to biomarker effects, gantenerumab reduced brain Aβ deposition and increased CSF Aβ42 levels, increased the Aβ42/40 ratio towards normal, reversed the course of CSF tau and phospho tau 181 levels towards normal, and slowed increases of NfL levels. Solanezumab increased total Aβ42 levels in CSF, but downstream AD markers did not show potentially beneficial changes and NfL showed greater increase. Although the trials did not meet their primary endpoints, the results of these DIAN-TU drug arms support the amyloid hypothesis in that for gantenerumab, the reduction of cerebral Aβ deposition led to a reversal of soluble tau pathophysiology. This demonstrates an effect of targeting Aβ on these “downstream” biomarkers and more importantly the possibility to interfere the Alzheimer pathological cascade. However, the studies remain short on evidence of the last chain of the amyloid hypothesis cascade, the link to clinical state. Further, it would be important to examine the distinct effect of these medications on different Aβ toxic mediators of the disease, such as the different Aβ oligomers, for a deeper understanding of trial results. Gantenerumab will be further investigated in an open label extension study to determine if further normalization of Aβ and AD downstream biomarkers can improve clinical and cognitive outcomes. Importantly, the biomarker outcomes of gantenerumab in the DIAN-TU-001 study also suggested that asymptomatic (CDR 0) participants had a larger magnitude of effect, supporting earlier interventions targeting Aβ.

A third DIAN-TU arm testing the BACE inhibitor atabecestat (JNJ-54861911)[27,44] was stopped because of hepatotoxicity that aborted development of this drug. Another DIAN-TU drug arm will soon begin and other drug arms are being planned, all likely testing tau targeting interventions in a combination approach (tau and Aβ). In terms of timing within the disease continuum, these trials are designed as secondary prevention trials focusing on the preclinical and early symptomatic disease stages. In this context, secondary prevention refers to prevention of symptomatic disease onset after Aβ biomarkers are positive. As in mildly symptomatic individuals, it can be expected that tau pathology is driving the clinical phenotype[30]. Tau-directed interventions may be effective in this population that includes early symptomatic phases of ADAD. Taking the results of the first two DIAN-TU drug arms into account, the ongoing API trial with crenezumab and the three planned tau drug arms of the DIAN-TU may be better positioned to provide a validation of the amyloid hypothesis by linking to cognition. Both API and DIAN-TU will provide a shared scientific resource of baseline and trial data and available biomarker samples in accordance with Collaboration for Alzheimer’s Prevention (CAP) principles providing opportunities to clarify the predictive, theragnostic, and prognostic roles of brain imaging and fluid biomarkers in AD prevention trials.[27,44]

As discussed for the secondary prevention design above, it is crucial to time the interventions and related read outs according to the disease phase they may address best. Knowledge on biomarker trajectories have enabled novel trial design concepts in ADAD aiming at biomarkers (figure A).In future biomarker-driven trial concepts potentially every clearly defined biomarker milestone along the ADAD disease trajectory could be used as inclusion criterion and every downstream biomarker milestone might serve as readout. However, changes in biomarker trajectories have to prove that they are contributing to delayed clinical onset. Furthermore, clinical trials will ultimately need to demonstrate a treatment's biomarker effects are at least "reasonably likely" to predict a clinical benefit (e.g., free from potentially confounding treatment effects unrelated to disease slowing and informative of a treatment's clinical effect), as some of the prevention clinical trials are seeking to demonstrate. These biomarkers might be accepted as a surrogate end point as proposed by the updated United States Food and Drug Administration guidelines on preclinical trials in AD[45] and recently employed to approve along an accelerated approval pathway the anti-Aβ immunotherapy aducanumab.

A primary prevention trial design also has been developed for the DIAN-TU.[46] The primary prevention design pursues the ultimate goal of delaying or preventing the development of AD-related pathology as measured by biomarkers rather than the prevention of associated phenotypes.[46] Ongoing design considerations for a primary prevention trial involve inclusion of cognitively unimpaired ADAD mutation carriers who are more than 11 years younger than EYO and therefore should have negative Aβ-biomarkers, but are destined to develop symptomatic AD because of their mutation carrier status[46] (figure A). Hence, these trial participants are in the Aβ-only phase of the disease where the mutations lead to altered APP processing alone without apparent downstream processes. Although challenging, the primary prevention trial will directly prove or reject the amyloid cascade hypothesis by sequentially measuring Aβ and non-Aβ biomarkers that are known to develop at specific periods of the disease prior to clinical symptoms develop and making decisions on the likelihood of significant disease modification and continuing treatment.

Future directions for ADAD trials include run-in and adaptive trial designs,[27] where longitudinally assessed individual data of potential trial participants prior to inclusion enables stratified inclusion for more homogeneous samples with respect to rates of change. This strategy could also make faster and more effective treatment arm adjustments during the course of the trial. Furthermore, the issue of practice effects is improved by using run-in data in AD prevention trials.[47] Cognitive run-in phases are currently ongoing for the next two DIAN-TU drug arms. Robust data from observational studies from the cognitively preclinical to the symptomatic disease phase will generate meaningful statistical power to foster the data exchange between ADAD observational trials and ADAD interventional trials in future.

Future interventions in ADAD might include other Aβ-directed immunotherapy approaches, including active immunization against Aβ epitopes.[48] Other Aβ-directed options include β-secretase- (BACE-) inhibitors with potentially less enzyme blockage than the previous interventions.[49,50] A similar approach to reduce Aβ production was pursued by developing γ-secretase inhibitors for LOAD but was abandoned due to significant side effects, including

infections and skin cancer.[51] Under development are γ-secretase modulators that aim to lower $A\beta_{1-42}$ without inhibition of total γ-secretase function.[52]

Therapies directed against pathologically aggregated microtubule-associated protein tau (MAPT or, in short, tau) are planned to be tested in ADAD in the DIAN-TU. Developments of novel assays for detection of tau in CSF and tau-specific PET tracers are ongoing.[30,31] A number of tau-based treatment approaches, which could be used in future ADAD trials, are being tested in phase I and phase II trials in LOAD. These approaches include passive immunization as well as active immunization[53]. Other therapeutic concepts such as reduction of tau expression (NCT03186989) and microtubule stabilization[53] are under development. Several broad spectrum anti-aggregants effective against tau aggregation are advancing in clinical and preclinical development in LOAD and other neurodegenerative diseases. The most advanced drug development in this class is on Leuco-methylthioninium bis-hydromethanesulfonate (LMTM, a.k.a. methylene blue), which inhibits aggregate formation of tau, TDP-43, prion protein, and Aβ, but failed to show clinical benefits in mild to moderate LOAD and FTD.[54] A potential reason for failure is limited blood brain barrier penetration, an issue shared with epigallocatechin gallate (EGCG), a natural broad spectrum anti-aggregant with effects on Aβ, α-synuclein and tau that was studied in Multiple System Atrophy.[55] Broad spectrum anti-aggregants are conceptually interesting for ADAD and LOAD as they potentially address the entire spectrum of pathological protein aggregates found in patients and therefore their effect might be less susceptible to timing. A range of next-generation broad spectrum anti-aggregants are being developed by various groups. Examples are NPT088, a fusion protein from g3p, a bacteriophage capsid protein with human IgG_1-Fc, that interacts with Aβ and tau[56] and anle138b, a small molecule with good BBB penetration and effects on oligomer formation of Aβ, α-synuclein, prion protein and tau.[57] Another promising future target is microglia activation, for which several drug development programs are on-going.[38]

Major challenges for the hypothesis

One obvious limitation of ADAD research is the scarcity of ADAD families.[21] Smaller sample sizes in clinical trials of ADAD compared to LOAD uniquely challenge power analyses as proven by the recently published results of the first two DIAN-TU drug arms.[25] The limited number of eligible participants necessitates large global networks,[27] with the exception provided by the existence of large, genetically isolated kindreds with ADAD mutations,[26] for outreach and recruitment that also require efforts in identification and involvement of rare kindreds. This challenge is addressed by the DIAN Expanded Registry (www.DIANXR.org). Further, study adherence and retention is pivotal as attrition may have more impact on power in trials with small sample sizes. Therefore, participant engagement is important because the relatively young ADAD family members often are employed, and many are raising children. An annual DIAN family conference provides the opportunity for global exchange within affected families, communication with researchers, and updates about the latest research advances. Additionally, novel adaptations such as home administration of therapies reduce travel burden and enhance retention. The Colombian API group also hosts annual informational meetings and social events for families with the *PSEN1 E280A* mutation to facilitate close communication with research participants.

These efforts may add to study adherence and biomarker completion rates in the ongoing treatment trials of the API[26] and the DIAN-TU.[27,44] The design of AD trials with preclinical ADAD individuals faces several ethical challenges, including whether to disclose mutation status to trial participants.[58] In a recent survey of individuals enrolled in the DIAN study attitudes were assessed regarding genetic testing for disclosure in clinical trials. The DIAN participants favored participation in trials even if it required that they learn their own genetic status but they preferred to self-determine whether to learn their status.[59] There may be circumstances when participants, Ethics Committees, and investigators determine that genetically blinded enrollment is preferred by specific cultural groups or populations.[26] Another challenge is assigning ADAD mutation carriers to placebo control groups.[60] The relative homogeneity of the ADAD population permits sharing of placebo groups between trials, particularly when relevant data from observational studies can be included. The common placebo group allows for a favorable randomization of active to placebo (i.e. 3:1) for each trial while benefiting statistical power through the addition of placebo from a concurrent trial (i.e. 3:2). For this reason, this approach has been employed in the DIAN-TU trial design reducing the number of mutation carriers that need to be assigned to placebo.[27] It is possible that carriers receiving active treatment will become aware of their genetic status should they experience secondary effects of the experimental drug being tested in the trial, thus disclosing that they have been assigned to an active treatment group. Appropriate informed consent should discuss the risks and benefits of participating, with emphasis on the fact that there are no existing effective interventions for AD, and that placebo control groups are needed for the validity of the study. Investigators conducting preclinical AD trials may also want to consider the implementation of open label extension studies, which may provide important complementary information on long-term safety and tolerability of experimental treatments in unimpaired individuals. Current interventional trials in ADAD invite participants in a wide age spectrum spanning up to 30 years and also diverse clinical status at baseline ranging from preclinical to mild dementia (table 1). This heterogeneity is a challenge for data analysis as change in biomarkers and rate of cognitive decline can be non-linear within individuals and based on different stages of the disease.[27] Therefore, both baseline values at study entry and the rate of change may differ among participants at different disease stages and not behave like in model predictions, as shown by the little to no decline in asymptomatic mutations carriers in the first DIAN-TU drug arms. A particular challenge was jointly analyzing both asymptomatic and symptomatic mutation carriers in the first two DIAN-TU drug arms rendering those trials to be only in part secondary prevention studies. For example, the developed model based on the DIAN observational study did not optimally predict and account for differences in variance on Mini Mental State Examination (MMSE) between asymptomatic and symptomatic mutation carriers in the trial. This effect lowers statistical power and increases the likelihood of missing a significant drug effect. Furthermore, cognitive changes, which are the primary read outs in the ongoing prevention trials, require special tools for sensitive detection of drug effects on subtle decline over time. To overcome these challenges, composite cognitive endpoints have been developed for the use in API and DIAN-TU and tested in datasets of observational studies.[21,22,24,27] Cognitive composites for the DIAN-TU and API ADAD offer sensitive and reliable tests that assess cognition in preclinical AD and the analysis is adjusted for subject-level years from symptom onset (EYO) and subject-level baseline cognitive performance (table 1), but

are still dependent on substantial drug effects to detect clear differences between treated and placebo groups in the asymptomatic phase of disease.[26,27] These cognitive composites need to be continuously improved to account for factors that reduce validity, such as a probable learning effect that may prevented decline in the logical memory delayed recall test, a subscale component of the DIAN-TU cognitive composite, in the recently completed DIAN-TU trials.

In mostly elder brains of LOAD individuals, multiple pathologies such as infarctions, arteriosclerosis, TDP-43 pathology, hippocampal sclerosis, and Lewy body pathology are present that may contribute to dementia [61] (table 2). This could be a key challenge for translating results from trials in symptomatic ADAD where beyond Aβ and tau only Lewy body pathology is present to LOAD. [39] This challenge for translation may not apply in such a way in the case of successful prevention therapies in ADAD as the prevention window for individuals with presymptomatic LOAD may also be in younger ages when the myriad of brain pathologies is not present yet.

Linkage to other major theories

Alternative hypothesis about the origin of LOAD such as accumulating DNA damage in the brain or myelin degradation, likely do not apply in ADAD where the mean age of symptomatic onset is 47 years. The amyloid-centric view of ADAD remains compelling because all ADAD-mutations lead to altered APP processing. However, it is increasingly obvious that also the other key players of ADAD and LOAD pathology such as tau-pathology, neuroinflammation[62] or Lewy body co-pathology deserve attention.

Major challenges for the role of ADAD as a model for therapy development in LOAD are two-fold i) the question regarding the comparability between ADAD and LOAD, and ii) the question on how trial and treatment design considerations can be transferred from a high-risk population to the general population. In brief, aside from age at onset and co-pathologies, the core AD phenotype, its clinical course, and neuropathology are virtually identical (table 2). For the transfer of the results to the general population several challenges have to be successfully overcome. Initial efforts are being made by collecting amyloid negative individuals with increased risk forx LOAD as determined by APOE genotype in the A3 trial or by investigating cognitively healthy amyloid positive individuals such as in the A4 trial.[27,46] Recently major progress has been made in the development of blood based amyloid assays.[36,63] These assays could be one way to identify individuals at risk to transfer progress in terms of therapy development in ADAD to LOAD. The most promising way to use trial and treatment concepts from ADAD in LOAD is via risk-enhanced sub-populations (figure B). Major efforts should be undertaken to develop and validate diagnostic techniques that could serve as screening tools to identify cognitively healthy individuals at an increased risk of developing AD. Further efforts should go in the direction of determination of precise individual risks and – once a therapy development program shows an effect – calculations should be performed based on the effect size of such treatments to develop risk score-based prevention algorithms.

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Conflicts of Interest

Johannes Levin 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, non-financial support from Abbvie and compensation for duty as part-time CMO from MODAG, outside the submitted work.

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References

1. Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends in pharmacological sciences. Oct 1991;12(10):383–8. doi:10.1016/0165-6147(91)90609-v [PubMed: 1763432]
2. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science. Apr 10 1992;256(5054):184–5. In File. [PubMed: 1566067]
3. Goate A, Chartier-Harlin MC, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature. Feb 21 1991;349(6311):704–6. doi:10.1038/349704a0 [PubMed: 1671712]
4. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature. Jun 29 1995;375(6534):754–60. Not in File. doi:10.1038/375754a0 [PubMed: 7596406]
5. Levy-Lahad E, Wasco W, Poorkaj P, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science. Aug 18 1995;269(5226):973–7. [PubMed: 7638622]
6. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. Jul 19 2002;297(5580):353–6. Not in File. doi:10.1126/science.1072994 [PubMed: 12130773]
7. Holtzman DM, Bales KR, Tenkova T, et al. Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A. Mar 14 2000;97(6):2892–7. Not in File. doi:10.1073/pnas.050004797 [PubMed: 10694577]
8. Lott IT, Head E. Dementia in Down syndrome: unique insights for Alzheimer disease research. Nat Rev Neurol. Mar 2019;15(3):135–147. doi:10.1038/s41582-018-0132-6 [PubMed: 30733618]
9. Jonsson T, Atwal JK, Steinberg S, et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature. Aug 2 2012;488(7409):96–9. doi:10.1038/nature11283 [PubMed: 22801501]
10. Arboleda-Velasquez JF, Lopera F, O'Hare M, et al. Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. Nature medicine. 2019/11/01 2019;25(11):1680–1683. doi:10.1038/s41591-019-0611-3
11. Makin S The amyloid hypothesis on trial. Nature. Jul 2018;559(7715):S4–s7. doi:10.1038/d41586-018-05719-4 [PubMed: 30046080]
12. Begley S The maddening saga of how an Alzheimer's 'cabal' thwarted progress toward a cure for decades. STAT Plus. June 25, 2019 2019:June 25, 2019.
13. Itzhaki RF, Lathe R, Balin BJ, et al. Microbes and Alzheimer's Disease. Journal of Alzheimer's disease : JAD. 2016;51(4):979–84. doi:10.3233/jad-160152 [PubMed: 26967229]
14. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in Early Alzheimer's Disease. New England Journal of Medicine. 2021;384(18):1691–1704. doi:10.1056/NEJMoa2100708 [PubMed: 33720637]
15. Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimer's research & therapy. 2021/04/17 2021;13(1):80. doi:10.1186/s13195-021-00813-8
16. Price JL, Ko AI, Wade MJ, Tsou SK, McKeel DW, Morris JC. Neuron number in the entorhinal cortex and CA1 in preclinical Alzheimer disease. Arch Neurol. Sep 2001;58(9):1395–402. Not in File. [PubMed: 11559310]
17. Karran E, Mercken M, Strooper BD. The amyloid cascade hypothesis for Alzheimers disease: an appraisal for the development of therapeutics. Review Article. Nat Rev Drug Discov. 08/19/online 2011;10:698. doi:10.1038/nrd3505 [PubMed: 21852788]
18. Honig LS, Vellas B, Woodward M, et al. Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease. The New England journal of medicine. Jan 25 2018;378(4):321–330. doi:10.1056/NEJMoa1705971 [PubMed: 29365294]
19. Blennow K, Zetterberg H, Rinne JO, et al. Effect of immunotherapy with bapineuzumab on cerebrospinal fluid biomarker levels in patients with mild to moderate Alzheimer disease. Archives of neurology. Aug 2012;69(8):1002–10. doi:10.1001/archneurol.2012.90 [PubMed: 22473769]

20. Abushouk AI, Elmaraezy A, Aglan A, et al. Bapineuzumab for mild to moderate Alzheimer's disease: a meta-analysis of randomized controlled trials. BMC Neurology. 2017/04/04 2017;17(1):66. doi:10.1186/s12883-017-0850-1 [PubMed: 28376794]
21. Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. The New England journal of medicine. Aug 30 2012;367(9):795–804. doi:10.1056/NEJMoa1202753 [PubMed: 22784036]
22. Fleisher AS, Chen K, Quiroz YT, et al. Associations between biomarkers and age in the presenilin 1 E280A autosomal dominant Alzheimer disease kindred: a cross-sectional study. JAMA neurology. Mar 2015;72(3):316–24. doi:10.1001/jamaneurol.2014.3314 [PubMed: 25580592]
23. Gordon BA, Blazey TM, Su Y, et al. Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: a longitudinal study. The Lancet Neurology. Mar 2018;17(3):241–250. doi:10.1016/s1474-4422(18)30028-0 [PubMed: 29397305]
24. McDade E, Wang G, Gordon BA, et al. Longitudinal cognitive and biomarker changes in dominantly inherited Alzheimer disease. Neurology. Oct 2 2018;91(14):e1295–e1306. doi:10.1212/wnl.0000000000006277 [PubMed: 30217935]
25. Salloway S, Farlow M, McDade E, et al. A trial of gantenerumab or solanezumab in dominantly inherited Alzheimer's disease. Nature medicine. 2021/07/01 2021;27(7):1187–1196. doi:10.1038/s41591-021-01369-8
26. Tariot PN, Lopera F, Langbaum JB, et al. The Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease Trial: A study of crenezumab versus placebo in preclinical PSEN1 E280A mutation carriers to evaluate efficacy and safety in the treatment of autosomal-dominant Alzheimer's disease, including a placebo-treated noncarrier cohort. Alzheimer's & dementia (New York, N Y). 2018;4:150–160. doi:10.1016/j.trci.2018.02.002
27. Bateman RJ, Benzinger TL, Berry S, et al. The DIAN-TU Next Generation Alzheimer's prevention trial: Adaptive design and disease progression model. Alzheimer's & dementia : the journal of the Alzheimer's Association. Jan 2017;13(1):8–19. doi:10.1016/j.jalz.2016.07.005
28. Simonsen AH, Herukka SK, Andreasen N, et al. Recommendations for CSF AD biomarkers in the diagnostic evaluation of dementia. Alzheimers Dement. Mar 2017;13(3):274–284. doi:10.1016/j.jalz.2016.09.008 [PubMed: 28341065]
29. Bateman RJ, Aisen PS, De Strooper B, et al. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. Alzheimer's research & therapy. Jan 6 2011;3(1):1. doi:10.1186/alzrt59
30. Gordon BA, Blazey TM, Christensen J, et al. Tau PET in autosomal dominant Alzheimer's disease: relationship with cognition, dementia and other biomarkers. Brain : a journal of neurology. Apr 1 2019;142(4):1063–1076. doi:10.1093/brain/awz019 [PubMed: 30753379]
31. Quiroz YT, Sperling RA, Norton DJ, et al. Association Between Amyloid and Tau Accumulation in Young Adults With Autosomal Dominant Alzheimer Disease. JAMA neurology. May 1 2018;75(5):548–556. doi:10.1001/jamaneurol.2017.4907 [PubMed: 29435558]
32. Barthélemy NR, Li Y, Joseph-Mathurin N, et al. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nature medicine. 2020/03/01 2020;26(3):398–407. doi:10.1038/s41591-020-0781-z
33. Sperling RA, Mormino EC, Schultz AP, et al. The impact of amyloid-beta and tau on prospective cognitive decline in older individuals. Annals of neurology. Feb 2019;85(2):181–193. doi:10.1002/ana.25395 [PubMed: 30549303]
34. Johnson KA, Schultz A, Betensky RA, et al. Tau positron emission tomographic imaging in aging and early Alzheimer disease. Ann Neurol. Jan 2016;79(1):110–9. Not in File. doi:10.1002/ana.24546 [PubMed: 26505746]
35. Koscik RL, Betthauser TJ, Jonaitis EM, et al. Amyloid duration is associated with preclinical cognitive decline and tau PET. bioRxiv. 2019:778415. doi:10.1101/778415
36. Ovod V, Ramsey KN, Mawuenyega KG, et al. Amyloid beta concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. Alzheimer's & dementia : the journal of the Alzheimer's Association. Aug 2017;13(8):841–849. doi:10.1016/j.jalz.2017.06.2266

37. Preische O, Schultz SA, Apel A, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. Nature medicine. Feb 2019;25(2):277–283. doi:10.1038/s41591-018-0304-3
38. Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. Apr 2015;14(4):388–405. doi:10.1016/S1474-4422(15)70016-5 [PubMed: 25792098]
39. Cairns NJ, Perrin RJ, Franklin EE, et al. Neuropathologic assessment of participants in two multi-center longitudinal observational studies: the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Dominantly Inherited Alzheimer Network (DIAN). Neuropathology. 2015 2015;35:390–400. On Request. [PubMed: 25964057]
40. Aisen PS. The potential of anti-inflammatory drugs for the treatment of Alzheimer's disease. Lancet Neurol. Sep 2002;1(5):279–84. [PubMed: 12849425]
41. Readhead B, Haure-Mirande JV, Funk CC, et al. Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus. Neuron. Jul 11 2018;99(1):64–82 e7. doi:10.1016/j.neuron.2018.05.023 [PubMed: 29937276]
42. Van Dam D, De Deyn PP. Non human primate models for Alzheimer's disease-related research and drug discovery. Expert opinion on drug discovery. Feb 2017;12(2):187–200. doi:10.1080/17460441.2017.1271320 [PubMed: 27960560]
43. Panza F, Seripa D, Lozupone M, et al. The potential of solanezumab and gantenerumab to prevent Alzheimer's disease in people with inherited mutations that cause its early onset. Expert Opin Biol Ther. Jan 2018;18(1):25–35. doi:10.1080/14712598.2018.1389885 [PubMed: 29037101]
44. Reiman EM, Langbaum JB, Tariot PN, et al. CAP—advancing the evaluation of preclinical Alzheimer disease treatments. Nature reviews Neurology. 09/29 2016;12(1):56–61. doi:10.1038/nrneurol.2015.177 [PubMed: 26416539]
45. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
46. McDade E, Bateman RJ. Stop Alzheimer's before it starts. Nature. Jul 12 2017;547(7662):153–155. doi:10.1038/547153a [PubMed: 28703214]
47. Jacobs DM, Ard MC, Salmon DP, Galasko DR, Bondi MW, Edland SD. Potential implications of practice effects in Alzheimer's disease prevention trials. Alzheimers Dement (N Y). Nov 2017;3(4):531–535. doi:10.1016/j.trci.2017.08.010 [PubMed: 29124111]
48. Vandenberghe R, Riviere ME, Caputo A, et al. Active Abeta immunotherapy CAD106 in Alzheimer's disease: A phase 2b study. Alzheimers Dement (N Y). Jan 2017;3(1):10–22. doi:10.1016/j.trci.2016.12.003 [PubMed: 29067316]
49. Timmers M, Van Broeck B, Ramael S, et al. Profiling the dynamics of CSF and plasma Abeta reduction after treatment with JNJ-54861911, a potent oral BACE inhibitor. Alzheimers Dement (N Y). Sep 2016;2(3):202–212. doi:10.1016/j.trci.2016.08.001 [PubMed: 29067308]
50. McDade E, Voytyuk I, Aisen P, et al. The case for low-level BACE1 inhibition for the prevention of Alzheimer disease. Nature reviews Neurology. Sep 21 2021;doi:10.1038/s41582-021-00545-1
51. Doody RS, Raman R, Farlow M, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. N Engl J Med. Jul 25 2013;369(4):341–50. doi:10.1056/NEJMoa1210951 [PubMed: 23883379]
52. Rynearson KD, Ponnusamy M, Prikhodko O, et al. Preclinical validation of a potent γ-secretase modulator for Alzheimer's disease prevention. J Exp Med. Apr 5 2021;218(4)doi:10.1084/jem.20202560
53. Panza F, Solfrizzi V, Seripa D, et al. Tau-based therapeutics for Alzheimer's disease: active and passive immunotherapy. Immunotherapy. Sep 2016;8(9):1119–34. doi:10.2217/imt-2016-0019 [PubMed: 27485083]
54. Gauthier S, Feldman HH, Schneider LS, et al. Efficacy and safety of tau-aggregation inhibitor therapy in patients with mild or moderate Alzheimer's disease: a randomised, controlled, double-blind, parallel-arm, phase 3 trial. Lancet (London, England). Dec 10 2016;388(10062):2873–2884. doi:10.1016/s0140-6736(16)31275-2 [PubMed: 27863809]
55. Levin J, Maass S, Schuberth M, et al. Safety and efficacy of epigallocatechin gallate in multiple system atrophy (PROMESA): a randomised, double-blind, placebo-controlled trial. The Lancet Neurology. Aug 2019;18(8):724–735. doi:10.1016/s1474-4422(19)30141-3 [PubMed: 31278067]

56. Levenson JM, Schroeter S, Carroll JC, et al. NPT088 reduces both amyloid-beta and tau pathologies in transgenic mice. Alzheimer's & dementia (New York, N Y). Sep 2016;2(3):141–155. doi:10.1016/j.trci.2016.06.004
57. Wagner J, Ryazanov S, Leonov A, et al. Anle138b: a novel oligomer modulator for disease-modifying therapy of neurodegenerative diseases such as prion and Parkinson's disease. Acta Neuropathol. Jun 2013;125(6):795–813. doi:10.1007/s00401-013-1114-9 [PubMed: 23604588]
58. Kim SY, Karlawish J, Berkman BE. Ethics of genetic and biomarker test disclosures in neurodegenerative disease prevention trials. Neurology. Apr 7 2015;84(14):1488–94. doi:10.1212/WNL.0000000000001451 [PubMed: 25762713]
59. Grill JD, Bateman RJ, Buckles V, et al. A survey of attitudes toward clinical trials and genetic disclosure in autosomal dominant Alzheimer's disease. Alzheimers Res Ther. 2015;7(1):50. doi:10.1186/s13195-015-0135-0 [PubMed: 26203303]
60. Peters KR, Lynn Beattie B, Feldman HH, Illes J. A conceptual framework and ethics analysis for prevention trials of Alzheimer Disease. Progress in neurobiology. Nov 2013;110:114–23. doi:10.1016/j.pneurobio.2012.12.001 [PubMed: 23348495]
61. Bennett DA. Mixed pathologies and neural reserve: Implications of complexity for Alzheimer disease drug discovery. PLOS Medicine. 2017;14(3):e1002256. doi:10.1371/journal.pmed.1002256 [PubMed: 28291788]
62. Suarez-Calvet M, Araque Caballero MA, Kleinberger G, et al. Early changes in CSF sTREM2 in dominantly inherited Alzheimer's disease occur after amyloid deposition and neuronal injury. Science translational medicine. Dec 14 2016;8(369):369ra178. doi:10.1126/scitranslmed.aag1767
63. Nakamura A, Kaneko N, Villemagne VL, et al. High performance plasma amyloid-beta biomarkers for Alzheimer's disease. Nature. Feb 8 2018;554(7691):249–254. doi:10.1038/nature25456 [PubMed: 29420472]
64. Kumar-Singh S Hereditary and sporadic forms of abeta-cerebrovascular amyloidosis and relevant transgenic mouse models. International journal of molecular sciences. Apr 23 2009;10(4):1872–95. doi:10.3390/ijms10041872 [PubMed: 19468344]
65. Jack CR Jr., Wiste HJ, Weigand SD, et al. Age-specific and sex-specific prevalence of cerebral beta-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50-95 years: a cross-sectional study. The Lancet Neurology. Jun 2017;16(6):435–444. doi:10.1016/s1474-4422(17)30077-7 [PubMed: 28456479]
66. Chhatwal JP, Schultz AP, Johnson K, et al. Impaired default network functional connectivity in autosomal dominant Alzheimer disease. Neurology. Aug 20 2013;81(8):736–44. doi:10.1212/WNL.0b013e3182a1aafe [PubMed: 23884042]
67. Ryman DC, Acosta-Baena N, Aisen PS, et al. Symptom onset in autosomal dominant Alzheimer disease: a systematic review and meta-analysis. Neurology. Jul 15 2014;83(3):253–60. doi:10.1212/wnl.0000000000000596 [PubMed: 24928124]
68. Vöglein J, Noachtar S, McDade E, et al. Seizures as an early symptom of autosomal dominant Alzheimer's disease. Neurobiology of aging. 2019/04/01/ 2019;76:18–23. doi:10.1016/j.neurobiolaging.2018.11.022 [PubMed: 30616208]
69. Vöglein J, Paumier K, Jucker M, et al. Clinical, pathophysiological and genetic features of motor symptoms in autosomal dominant Alzheimer's disease. Brain : a journal of neurology. 2019;142(5):1429–1440. doi:10.1093/brain/awz050 [PubMed: 30897203]
70. Vöglein J, Kostova I, Arzberger T, et al. Seizure prevalence in neurodegenerative diseases-a study of autopsy proven cases. Eur J Neurol. Jan 2022;29(1):12–18. doi:10.1111/ene.15089 [PubMed: 34472165]
71. Vöglein J, Ricard I, Noachtar S, et al. Seizures in Alzheimer's disease are highly recurrent and associated with a poor disease course. Journal of neurology. Oct 2020;267(10):2941–2948. doi:10.1007/s00415-020-09937-7 [PubMed: 32488295]
72. Jack CR Jr., Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. Feb 2013;12(2):207–16. In File. doi:10.1016/S1474-4422(12)70291-0 [PubMed: 23332364]

73. Vöglein J, Kostova I, Arzberger T, et al. First symptom guides diagnosis and prognosis in neurodegenerative diseases-a retrospective study of autopsy proven cases. Eur J Neurol. 2021;28(6):1801–1811. [PubMed: 33662165]

Research in Context

Systematic review:

The authors reviewed literature including PubMed, meeting abstracts and company press releases. Clinical phase III trials with investigational disease-modifying drugs, many targeting Aβ, have not demonstrated consistent clinically meaningful benefits. This has triggered an ongoing debate about the validity of the amyloid cascade hypothesis for AD.

Interpretation:

Our updated hypothesis states that anti-Aβ investigational therapies are likely to be most efficacious when initiated in the preclinical (asymptomatic) stages of AD when the disease is driven primarily by amyloid pathology and prior to irreversible initiation of downstream effects.

Future directions:

The modified amyloid cascade hypothesis pertaining to the preclinical stage of AD, still needs to be integrated with the development and consequences of co-pathology like the ubiquitous tauopathy and other typical co-pathologies. Interventions in cognitively unimpaired individuals at ultra-high risk for dementia such as ADAD mutation carriers, during amyloid-only and pre-amyloid stages (i.e., prior to substantial other pathologies), represent the ideal population to evaluate the efficacy of putative disease-modifying Aβ therapies in a biomarker-defined window of opportunity and, thus, test the amyloid cascade hypothesis.

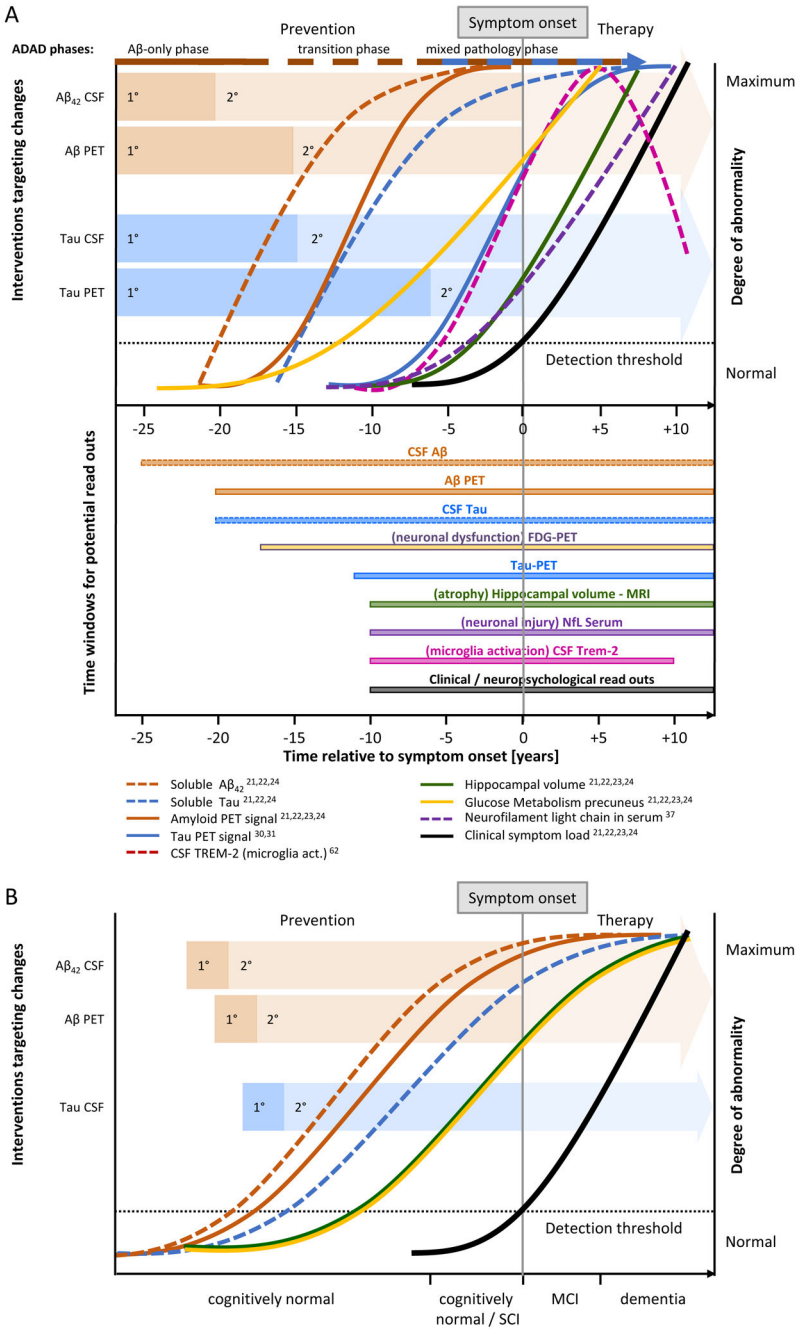

Figure:

Clinical- and biomarker-changes and windows of opportunities for interventions and read-outs in clinical trials

A) The figure shows approximate biomarker trajectories based on data from API and DIAN or both, if available (upper panel) in ADAD. Windows of opportunity for targeted intervention aiming at treatment, secondary (2°) and primary (1°) prevention are indicated (upper panel). Primary prevention is possible until the targeted biomarker crosses the detection threshold towards abnormality and secondary prevention from this point on until symptom onset. The lower panel indicates putative windows for the detection of biomarker

changes in treatment trials. We assumed that this time interval starts five years prior to significant biomarker changes at group levels. Additionally on top of the panel the authors indicate phases of the driving elements in distinct phases of ADAD based on their discretion. B) The figure is adapted from Jack and colleagues[72] and aims to show the same timelines for interventions according to the respective biomarkers in LOAD.

Table 1

Ongoing clinical trials with ADAD mutation carriers

Study	API ADAD Colombia Study	DIAN-TU - drug arm 1 and 2
Participants	168 cognitively unimpaired ADAD carriers and 84 non-carriers from the Colombian *PSEN1 E280A* kindred (aged 30-60 years). All non-carriers are assigned to placebo.	144 ADAD (*PSEN1*, *PSEN2*, or *APP*) - mutation carriers and 49 non-carriers; 15 years prior to 5 years after estimated age of symptom onset (aged 18-80 years). All non-carriers are assigned to placebo.
Trial concept	Secondary prevention (Aβ pathology is likely, no demented participants included).	Secondary prevention / treatment (Aβ pathology is likely, cognitively healthy participants and participants with mild dementia included).
Duration and main inclusion criteria	260 weeks; membership in *PSEN1* E280A mutation carrier kindred, without MCI or AD; MMSE >26 (changed to MMSE of >24 for participants with <9 years of education, or MMSE of >26 for those with >9 years of education).	112 weeks biomarker trial followed by 148 weeks adaptive prevention trial: Total 260 weeks; ADAD family history, with a diagnosis of either cognitively unimpaired, MCI, or mild dementia; global CDR of not more than 1.0.
Compound and administration	Crenezumab SC every 2 weeks or optional IV every 4 weeks.	Two drug arms with gantenerumab SC every 4 weeks, and solanezumab IV every 4 weeks, respectively
Drug targets	Oligomeric & fibrillar Aβ (crenezumab).	Aggregated Aβ (gantenerumab). Monomeric Aβ (solanezumab).
Primary Outcomes	Change in the API ADAD composite cognitive test score derived from elements of the Mini–Mental State Examination (MMSE) Orientation to Time, CERAD Word List Delayed Recall, CERAD Constructional Praxis, the Multilingual Naming Test (MINT), and Ravens progressive matrices (set A).	Change in the DIAN-TU cognitive composite score. The DIAN-TU cognitive composite includes: The International Shopping List Test Delayed Recall, the WMS-Logical Memory Delayed Recall, the WAIS-R Digit Symbol Coding, and the MMSE total score.
Biomarker measures	Florbetapir PET,18F-FDG-PET, MRI, CSF/plasma, Tau-PET pending.	CSF/plasma, florbetapir PET, PiB-PET, MRI.
Timelines	Recruitment started in 2013. Estimated study completion date is 2022.	Recruitment started in 2012. Randomized study completion in 2019, with OLE of gantenerumab through 2024.
Interim analyses	No interim analysis.	Biomarker analyses based on adaptive design last participant completes 104 weeks of treatment.
Results	Trial not completed yet.	Negative on primary outcome. Gantenerumab improved amyloid and tau imaging and fluid AD biomarkers and NFL towards normal. Solanezumab bound soluble Aβ and changed NFL towards abnormal.

Abbreviations: ADAD, autosomal dominant AD; API, Alzheimer Prevention Initiative; DIAN-TU, Dominantly Inherited Alzheimer Network-Trials Unit; *PSEN1*, *presenilin 1*; *PSEN2*, *presenilin 2*; *APP*, gene encoding the amyloid precursor protein; Aβ, amyloid β ; MCI, mild cognitive impairment; AD, Alzheimer disease; MMSE, mini mental state examination; CDR®, Clinical Dementia Rating®; SC, subcutaneous; IV, intravenous; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; WMS, Wechsler memory scale; WAIS-R, revised Wechsler adult intelligence scale; PET, positron emission tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; PiB; Pittsburgh compound B.

Table 2:

Comparison between autosomal dominant Alzheimer disease and sporadic Alzheimer disease

	Autosomal dominant Alzheimer disease	**Sporadic Alzheimer disease**
Clinical cognitive presentation (early predominant) [21,65,73]	typical amnestic, atypical non-amnestic	typical amnestic, atypical non-amnestic
Clinical non-cognitive presentation [24,65,68,69,70,71]	motor symptoms, seizures, myoclonus, hallucinations *	motor symptoms, seizures, myoclonus, hallucinations
Neuropsychological profile [21,65]	memory disturbance, visuospatial deficits, executive dysfunction, generalized cognitive decline	memory disturbance, visuospatial deficits, executive dysfunction, generalized cognitive decline
Cognitively presymptomatic neuropsychological changes [21,24,65]	learning-memory and executive function decline up to 12 years before symptom onset	learning-memory and executive function decline up to 12 years before symptom onset
Mean age of onset [67]	mid 40s	70s
Disease duration [21,65]	approximately 10 years on average	approximately 10 years on average
Structural MRI [21,23,24]	early hippocampal, parietal, and angular gyrus atrophy; later whole brain atrophy	early hippocampal, parietal, and angular gyrus atrophy; later whole brain atrophy
Functional MRI [66]	impaired default mode network	impaired default mode network
Aβ-PET [21,23,24,65]	cortical Aβ deposition, early basal ganglia pattern of Aβ deposition	cortical Aβ deposition
FDG-PET [21,23,24]	parieto-temporo-occipital hypometabolism	parieto-temporo-occipital hypometabolism
Tau-PET (only preliminary findings) [30,31]	prominent tracer uptake in entorhinal, temporal lobe and precuneus	prominent tracer uptake in temporal lobe
CSF $A\beta_{1-42}$ [21,24]	decreased by 50%	decreased by 50%
CSF tau [21,24]	increased by 2-3 fold	increased by 2-3 fold
Neuropathology [39]	Aβ plaques, then tau tangles; Lewy bodies, cerebral amyloid angiopathy common **; higher burden of AD pathology, more diffuse Aβ plaques ***	Aβ plaques, then tau tangles; Lewy bodies, cerebral amyloid angiopathy common; non-AD pathologies TDP-43, argyrophilic grain disease, hippocampal sclerosis, and infarcts

Abbreviations: MRI, magnetic resonance imaging; Aβ, amyloid β; PET, positron emissions tomography; FDG, fluorodeoxyglucose; CSF, cerebrospinal fluid; AD, Alzheimer disease; TDP, TAR DNA-binding protein.

* spastic paraparesis and cerebellar ataxic phenotypes have been described.

** Individuals with ADAD due to *APP* triplications or certain *APP* mutation are at an increased risk for CAA and therefore for lobar cerebral hemorrhages. Certain *APP* mutations have been linked with little to no neurofibrillary tau pathology[64]

*** A high cerebellar Aβ plaque load was reported in specific mutations, but also in early-onset “sporadic” AD.