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PERSPECTIVE

The case for regulatory approval of amyloid-lowering immunotherapies in Alzheimer's disease based on clearcut biomarker evidence

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Abstract

Decades of research have provided evidence that Alzheimer's disease (AD) is caused in part by cerebral accumulation of amyloid beta-protein (Aβ). In 2023, the US Food and Drug Administration gave full regulatory approval to a disease-modifying Aβ antibody for early AD. Secondary prevention trials with Aβ antibodies are underway. We summarize peer-reviewed evidence for targeting Aβ and argue that regulators should consider approving new agents working by similar mechanisms (Aβ antibodies and vaccines) based on robust amyloid lowering and reasonable safety. The urgent need to provide treatments to millions of mildly symptomatic patients suggests that AD should join other diseases for which standard approval is based on significant changes in mechanistically meaningful biomarkers coupled with safety. Robust amyloid lowering in secondary prevention trials of people who have amyloid plaques but are asymptomatic could also provide evidence of a change in the pathophysiological progression of AD as a basis for regulatory approval.

KEYWORDS
active vaccines, Alzheimer's disease, Alzheimer's disease prevention, amyloid beta protein, disease modification, immunotherapy, monoclonal antibodies, regulatory policy, surrogate markers, treatment

Highlights

- Thirteen key findings support amyloid beta as a cause of Alzheimer's disease (AD).
- Three immunotherapies lower amyloid and slow decline, allowing regulatory approval.
- New such agents could be considered for approval due to amyloid lowering and safety.
- Urgency suggests AD may join diseases with approval due to a key biomarker + safety.

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common cause of age-related intellectual failure, slowly robbing its victims of their most human qualities—reasoning, abstraction, memory, judgment, and equanimity. This devastating decline ultimately leads to a complete loss of functional independence and premature death.[1] The impact of AD extends well beyond the individual, placing tremendous burdens on families, and it poses an existential challenge to health and social care systems.[2] Globally, AD affects some 60 million patients.[3] This number does not include the estimated > 6-fold people who unknowingly harbor the disease in its presymptomatic biological form.[4] Although the last 2 years have witnessed the advent of the first disease-modifying treatments that lower one pathological hallmark of sporadic AD (amyloid plaques) and appear to lessen the other (abnormal forms of tau protein), leading to slower rates of cognitive decline,[5–8] there remains an urgent need to accelerate the development and dissemination of additional biologically and clinically effective therapeutics for this enormous challenge to personal and public health.

Evidence from many laboratories and clinics over 4 decades supports the hypothesis of an early and necessary pathogenic role of amyloid beta (Aβ) protein accumulation in the initiation and progression of AD.[9–13] This perspective asks the question of whether robust removal of amyloid from patients' brains constitutes sufficient evidence of a fundamental slowing of AD pathobiology that is predictive of the subsequent avoidance or lessening of the disease's cognitive and functional symptoms. We present evidence and arguments in support of this premise and examine some opposing points of view. The Perspective is intended to stimulate discussion and debate among regulators, clinicians, scientists, and members of the lay public concerned about accelerating access to disease-modifying treatments for sporadic AD.

Addressing this question of the usefulness of amyloid lowering as a surrogate indicator for slowing clinical progression is also relevant to the related goal of primary or secondary prevention of AD.[14] Primary prevention trials enroll persons at high risk of developing the biological and clinical manifestations of the disease but who have neither when enrolled. Secondary prevention trials enroll persons who already have the biological manifestations of AD (e.g., amyloid plaques) but do not yet have the clinical symptoms. As we address the key question raised in the title of this article, we may also inform whether robust prevention or secondary lowering of amyloid deposition could provide sufficient evidence of later clinical benefit.

Before laying out our arguments for amyloid as a key surrogate marker for future AD immunotherapy approvals, the authors would like to indicate that in addition to our full disclosures of potential conflicts of interest, we acknowledge to all readers that academic–industry collaborations, while useful and necessary for a therapeutic field, can influence an expert's view of the drug development process and its outcomes. Our shared opinions here are provided in the context of the "gold standard" that enables medical specialists to participate in public discussions of emerging and unsettled clinical issues, namely, full disclosures of potential conflicts of interest by all authors so that readers can make their own judgements about potential biases.

Foundational observations support the amyloid hypothesis of AD[10,11] and provide the basis for the position of this perspective. Many experts on AD, though not all, agree with the accuracy of the following evidence-based and peer-reviewed scientific observations that are relevant to familial and sporadic forms of the disease.

1. People with AD undergo progressive Aβ deposition intimately associated with neuritic, microglial, and astrocytic cytopathology in brain regions serving memory and cognition.[1,15] A century of research has led to a universally accepted definition of AD as a dementia marked by cerebral amyloid plaque and neurofibrillary tangle formation.[4]
2. The amyloid precursor protein (*APP*) gene is on chromosome 21q.[16] In trisomy 21 (Down syndrome [DS]), patients show very early diffuse plaques of Aβ (beginning ≈ age 10–15 years) followed by a typical progression of AD neuropathology.[17] This has been shown to be caused by the increased gene dosage of wild-type *APP*: rare translocation DS cases in which the translocated 21q fragment is telomeric to (and therefore lacks) the *APP* gene can live into late life with few amyloid plaques and little AD neuropathology.[18]
3. Analogous to the mechanism in trisomy 21, humans without DS who have an inherited microduplication of a small region of chromosome 21q containing the *APP* gene develop typical AD with cerebral amyloid angiopathy at an early age.[19]
4. Autosomal dominant AD is caused by missense mutations in either the substrate (*APP*) or the protease (presenilin/γ-secretase) of the biochemical reaction that generates Aβ throughout life, thereby enhancing amyloid formation.[20–23]
5. There is an inverse linear correlation between the degree to which AD-causing presenilin mutations raise the long Aβ/short Aβ ratio (i.e., shift Aβ production to longer, more amyloidogenic peptides) and the age of symptom onset.[24,25] In this context, many features of the known genetic forms of AD resemble accelerated forms of "sporadic" AD both biologically and clinicopathologically, but the significance of this relationship has been debated in the field, and findings in familial AD cannot automatically be extrapolated to all sporadic AD cases.
6. A rare *APP* missense mutation that alters the Aβ sequence to decrease *APP* cleavage by β-secretase and thereby lowers Aβ production by ≈ 30% throughout life prevents the development of AD and AD-like cognitive decline in late life.[26] For example, one such mutation carrier survived to age 104 with no AD symptoms and was found to have very little amyloid deposition upon autopsy.
7. Apolipoprotein E (*APOE*) ε4 is the major genetic risk factor for sporadic (late-onset) AD worldwide. Among its potential pathogenic effects, *APOE* ε4 has been shown to increase Aβ aggregation and decrease Aβ clearance from the brain, leading to accelerated Aβ accumulation and typical AD neuropathology.[27,28] *APOE* ε4 homozygotes have a particularly high likelihood of having

abnormal AD biomarkers, including robust Aβ deposition, and developing symptoms of AD.[29]

8. Diffusible Aβ oligomers (oAβ) isolated from the brains of sporadic AD patients have been shown to induce neuritic dystrophy and AD-type tau hyperphosphorylation in rodent hippocampus and induced pluripotent stem cell–derived human neurons.[30,31] Moreover, in vivo injection of oAβ isolated from sporadic AD cerebral cortex into the brains of healthy adult rats impairs their memory function.[30] Neutralizing and lowering diffusible oAβ may be an additional benefit of some amyloid plaque–clearing agents.[6]
9. Human biomarker studies show that falling cerebrospinal fluid (CSF) levels of soluble Aβ42 monomers (signifying Aβ42 aggregation and deposition in cerebral amyloid plaques) precedes rising CSF tau levels, decreased brain metabolism on fluorodeoxyglucose (FDG) positron emission tomography (PET), tau regional spread seen on tau PET, evidence on volumetric magnetic resonance imaging (vMRI) of brain atrophy, and cognitive decline. Such sequences of biomarker changes, reported in both familial and sporadic AD subjects,[12,13] are consistent with the amyloid hypothesis.
10. Completed and published clinical trial data show that three different Aβ monoclonal antibodies can robustly clear amyloid plaques and lower certain tau biomarkers and glial fibrillary acidic protein (GFAP) levels in CSF and plasma of sporadic AD patients. This reduction of plaque pathology is significantly associated with less decline in cognition and function (e.g., activities of daily living) in comparisons across treatment groups.[5–7] While the clinical meaningfulness of benefit in completed 18-month trials has been debated, data from the phase 3 trial of lecanemab and its ongoing open-label extension indicate that AD patients entering the trial with low levels of tau deposition confined to the medial temporal lobe experienced either stabilization of cognitive decline or mild symptomatic improvement.[32,33] It should be noted that correlations reported to date are at a group level; there are few or no published reports of correlations in immunotherapy trials between decreases in amyloid PET and cognitive and functional scores at an individual level. As one potential example of a biomarker correlation seen at an individual level, more rapid decreases of amyloid PET in a donanemab trial were associated with those trial participants who had greater slowing of tau accumulation.[7]
11. Pharmacological lowering of amyloid deposits in certain systemic organs (e.g., transthyretin amyloid in familial and sporadic cardiac amyloidosis) is associated with significantly decreased organ failure and fewer clinical symptoms.[34]
12. Progressive amyloidosis (such as occurs invariably in AD) has been proven in many diverse studies to be detrimental to organ function. In accord, immune-mediated removal of cortical amyloid plaques in AD patients has been shown by subsequent *post mortem* analysis to have ameliorated peri-plaque tau neuritic dystrophy.[35]
13. A portion of older adults die with substantial cerebral amyloid deposition but relatively little neuronal and glial injury or cognitive dysfunction, which is consistent with the presymptomatic phase of amyloid accumulation ≈ 10 to 20 years before symptom onset. Some such individuals may have benefitted from little-understood forms of biological resilience and/or cognitive reserve.[36] The long prodromal period between amyloid accumulation and symptom onset means it is to be expected that a portion of humans will die with substantial cerebral amyloid in the absence (so far) of cognitive decline.

For almost 50 years, there has been vigorous academic debate about whether amyloid accumulation causes AD (as supported by the genetic evidence in points 2–6 above) and whether amyloid plaque clearing is an advantageous approach to treatment (as supported by the trial data in sporadic AD described in point 10). The recent placebo-controlled trials of plaque-lowering monoclonal Aβ antibodies provide objective evidence in thousands of treated patients with sporadic AD that neuropathological and clinical benefits can occur with robust removal of amyloid plaques, at least to some extent.[5–7] Although some phase 3 Aβ antibody trials were negative (e.g., the interrupted ENGAGE trial of aducanumab), these trials did not robustly clear plaques down to near normal levels (< 15–20 Centiloid [CL]), a change that appears to be required to achieve clinical benefit.[8] While many AD clinicians agree that the extent and meaningfulness of the benefits for disease progression observed to date must be improved, there is emerging evidence that treatment with amyloid-clearing antibodies early in the clinical course of sporadic AD is associated with a slowing of biological progression and, most importantly, a reduction in cognitive and functional worsening.[2,8] For example, follow-up analyses of patients in the CLARITY AD phase 3 trial of lecanemab, including in its open-label extension, have suggested that 18 to 24 months of treatment of patients who at trial entry had relatively low levels of pathological tau (confined to the medial temporal lobe) and/or relatively low (but still abnormal) levels of amyloid plaque burden on PET (< 60 CL) were each associated with either stabilization of cognitive trajectory (no worsening) or a modest degree of improvement in scores.[32] Also relevant to establishing a useful threshold for the degree of amyloid lowering are trial data on gantenerumab in either sporadic or autosomal dominant AD that demonstrated (1) those individuals with the most robust amyloid reduction ("responders") had evidence of clinical, cognitive, and biomarker benefit,[37] and (2) asymptomatic individuals treated for the longest period with gantenerumab may have an up to 50% reduction in the risk of developing dementia.[38,39] While these data suggest that very early treatment or presymptomatic (secondary) prevention could produce substantially greater clinical benefits for disease progression,[4] further confirmation of such outcomes is needed.

An oft-voiced concern about amyloid lowering as an approach to AD is the impression of many failed anti-amyloid trials in past years. The most likely reason for the impression that numerous earlier trials putatively targeting amyloid had failed is that they either did not yet have methods available to quantify brain amyloid burden in vivo, that is, before amyloid PET (e.g., alzhemed [taurine variant]; scyllo-inositol) or they did not find evidence of amyloid lowering below baseline levels (e.g., solanezumab).[40] There are published lists of numerous such failed "anti-amyloid" trials that could not or did not measure significant drug

effects on brain amyloid levels, that is, did not confirm target engagement (see e.g., Haas and Selkoe[41]—Table 2.)[42,43] Until the recent trials of amyloid-lowering monoclonal antibodies that required amyloid PET for both trial entry and outcome, one could not be certain whether amyloid lowering per se could affect clinical outcomes. Thus, many earlier "amyloid trials" cannot be definitively concluded to have failed.

Based on the recent trials of three anti-amyloid immunotherapies (the EMERGE but not the ENGAGE trial of aducanumab, and the phase 3 trials of lecanemab and donanemab), the AD field has recognized that a marked reduction of fibrillar brain amyloid levels is associated with clinical benefit in early AD.[4,41,44] Conversely, those immunotherapy trials that did not succeed in substantially reducing amyloid plaque levels from baseline (e.g., solanezumab, crenezumab, gantenerumab) did not achieve significant clinical benefit (at least in the time frame of the trial). Indeed, robust amyloid plaque reduction is currently an obligatory criterion in the US Food and Drug Administration (FDA)'s Accelerated Approval pathway for AD disease-modifying agents. The aforementioned genetic, neuropathological, and biomarker evidence that Aβ accumulation can initiate AD, at least in many cases, supports our thesis that agents that substantially reduce brain amyloid burden and thereby lower some abnormal forms of tau and astrocytosis (i.e., lower plasma GFAP levels) are slowing the key pathogenic lesions of AD. These findings suggest that preventing the formation of amyloid deposits (primary prevention) or lessening further accumulation of amyloid in presymptomatic individuals (secondary prevention) could delay or prevent the onset of AD symptoms.

If one asks the long-standing question "What causes AD?," one can cite objective, confirmed evidence that autosomal dominant AD, AD in DS, and "sporadic" AD accelerated by *APOE* ε4 inheritance are all plausible examples of Aβ accumulation as an initiator of AD.[2] Even though the upstream molecular causes of amyloid deposition in many sporadic AD cases cannot yet be specified, all of these cases include prominent, progressive amyloid build-up that is very likely to contribute to abnormal brain biology and cognitive dysfunction. We should also note the numerous parallels between familial (dominant) and sporadic AD, for example, the occurrence in both of certain shared comorbidities such as Lewy body pathology and white matter hyperintensities.[45,46]

The growing recognition of a precipitating role of abnormal Aβ42 accumulation moves the amyloid-clearing approach beyond combating symptoms to a slowing of the etiological process.[41] Assuming further evidence, particularly in clinical practice, shows that anti-amyloid antibodies (and later other biologics and small molecules) slow both the seminal pathology of AD and its symptoms, we should redefine this approach as not just treating symptoms but lessening the biological progression of the disease. In this context, when we interpret well-conducted, statistically rigorous (and substantially safe) amyloid-lowering trials, we should recognize that we are interfering with a fundamental cause and mechanism of AD. This reasoning represents a conceptual shift: we should consider in our evaluation of such amyloid-targeting trial outcomes that the agent demonstrably inhibited a causative biological process. In this sense, evidence of robust amyloid lowering combined with biomarker evidence of other biological benefits, for example, less soluble tau/phosphorylated tau (p-tau), less microglial inflammation, and less astrocytosis (GFAP), that could contribute to accelerated approval by FDA criteria should, in our view, also support standard (traditional) approval based on robust plaque lowering (to < 15–20 CL) as a surrogate for future cognitive benefit. This approach could substantially reduce the time needed to gain regulatory approval and clinical access to therapies that impact the underlying pathobiology of AD. It does not preclude the post-marketing collection of data on the relationship between amyloid plaque effects and clinical outcomes. However, we acknowledge that this conceptual shift is the shared goal of the authors of this Perspective, but some regulators and clinicians have voiced questions about whether there is suitable evidence to justify this change in approach.

In ongoing analyses of multiple AD biomarkers, robust amyloid removal (to < 20 CL) has demonstrated beneficial effects on some, but not all, AD pathophysiological processes. Some of these biomarkers either measure directly (e.g., soluble Aβ42 levels in fluids) the amyloid aggregation state or indirectly the reactions to amyloid (e.g., certain p-tau species), and these can be substantially improved by amyloid removal. Other biomarkers measure tau tangles (tau PET), reactions by glial cells (e.g., GFAP from astrocytes), or neurodegeneration (e.g., release of neurofilament light protein) and are variably improved or stabilized by amyloid removal. We propose that the fluid biomarkers of AD can also serve alongside robust amyloid lowering by PET scan as surrogate measures predicting future clinical benefit, with the added advantage of being able to deliver broad patient access to those fluid biomarkers that can be quantified in blood.

There are important precedents from other fields of medicine that support the arguments made here. Perhaps the most well-known and oft-cited example is that of the FDA and European Medicines Agency (EMA) approvals of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors to lower low density lipoprotein (LDL) cholesterol in the mid-1980s, well before there was definitive clinical evidence that these approved agents significantly slowed or prevented clinical events from atherosclerotic cardiovascular disease (ASCVD). The first such agent to be approved was lovastatin (mevocor), and regulatory approval and launch of others soon followed. The obvious justification offered was that the epidemiological evidence that elevated LDL cholesterol levels, whether for genetic or dietary reasons, led to a higher likelihood of heart attacks and strokes made it reasonably likely that clinical benefit would follow treatment. These approvals, based on strong biomarker effects signifying interference with a fundamental biological feature of a disease, can be likened to what has recently emerged in the field of AD, as discussed above. In the case of the regulatory approval of cholesterol-lowering drugs, some argued at the time that ASCVD was a complex, multifactorial disease process that involved pathogenic changes beyond cholesterol deposition before clinically meaningful vascular dysfunction occurred. Nevertheless, biological evidence from many laboratories, clinics, and companies worldwide strongly supported the concept that avoiding further cholesterol deposition would help prevent disabling or fatal clinical outcomes.

In this context, many experts in the biology of AD agree that Aβ accumulation and amyloid deposition in plaques and vessels is an important

contributor to the clinical development of AD, even in cases in which it is not formally causative. The most compelling such argument from a regulatory perspective can be made for new agents in the same therapeutic class as those that have been conventionally approved based on combined biomarker and clinical outcomes, for example, anti-amyloid antibodies. If a new molecule in this class shows robust and significant amyloid removal (potentially targeted to < 20 CL by amyloid PET, a level considered to be in the normal range), accompanied by a detailed and acceptable safety profile, it should be allowed regulatory approval so as not to delay its availability for the myriad patients experiencing a progressive, ultimately fatal neurological disease. On the other hand, for agents that lower amyloid by a distinct molecular mechanism, the first such examples might be expected to achieve both biomarker and clinical benefits before full regulatory approval and launch.

Several arguments have been expressed against the amyloid hypothesis and the amyloid-related perspective presented here. One argument against our position that can be—and has been—raised is that amyloid lowering per se does not necessarily interfere with an obligatory dysfunctional process of AD. However, the multiple lines of widely accepted biological evidence reviewed earlier (points #1–13), coupled with the recent, peer-reviewed clinical trial results of plaque-removing antibodies,[5–7] contradict this argument. Related to this argument, the degree of clinical benefit derived from amyloid removal is likely to be dependent on several factors, including disease stage, cause of disease (e.g., DS), and extent of comorbidities.[8] For example, removing amyloid in more advanced clinical and neuropathological AD has been shown to have little benefit.[7,32] Continued exploration of which amyloid species (e.g., fibrillar plaques and/or diffusible oligomers/protofibrils) best predict clinical outcomes will be important.[4]

A second counterargument suggests that the evidence for amyloid clearing to date is insufficiently meaningful from a patient and family perspective so it is premature to consider traditional regulatory approval of a new agent in the same class based on robust amyloid lowering alone. While some authorities will continue to put this argument forward, the latest analyses of phase 3 trial data suggest that at least a substantial portion of AD patients (e.g., those early in their tauopathy phase) treated for > 18 months with amyloid-clearing antibodies do achieve a degree of slowing and sometimes arrest of clinical progression[32,33] that is desirable and meaningful to patients and families, as supported by published trial data on formal scales of caregiver burden.[6] Moreover, published analyses have quantified the "time saved" by patients (i.e., delay to a specified further loss of function) when treated with approved amyloid-lowering therapies.[4]

A third argument against the position advocated here is that the clinical benefit reported in anti-Aβ antibody trials is a largely spurious or "placebo" (non-biological) effect.[47] That is, it is principally due to functional unblinding experienced by patients and clinicians during the trial upon the occurrence of amyloid-related imaging abnormality edema (ARIA-E) detected on MRI. There are at least three published reasons this perspective is not tenable. First, special efforts were made to prevent unblinding during the trials, for example, clinical evaluations were performed by independent raters who had no knowledge of the patient's radiographic and symptomatic results to date.[6,7] Second, sensitivity analyses of the reported trial data in peer-reviewed articles have not supported a statistically significant influence of ARIA-E on the trial outcomes—the benefit is realized whether the patient had ARIA or not.[6,33] Third, in the example of the CLARITY AD trial of lecanemab, the size and statistical significance of both the biomarker effects and the four clinical outcomes were robust and consistent enough to be unlikely to have arisen solely from unblinding from the asymptomatic ARIA-E that occurred in ≈ 13% of treated patients, with only 2.8% having any symptoms the patient noticed.[6]

Pending further analyses from the recent phase 3 trials and their open-label extensions, we believe it is highly likely that the FDA-approved Aβ antibodies to date have meaningful effects on the cognitive and functional trajectories of AD over time. Importantly, there has been essentially no disagreement voiced to the fact that three approved Aβ antibodies (aducanumab, lecanemab, donanemab) significantly lowered the amyloid plaque burden in a large majority of treated trial participants. Even as providers continue to closely monitor the clinical impact and safety of these agents and others to come, the achievement of robust (and generally reasonably safe) amyloid lowering should be viewed as a substantial interference with the progressive pathobiology of AD.

Importantly, accepting such a regulatory paradigm shift would still require the eventual provision of clinical data on efficacy as well as safety, similar to the process in the FDA's current accelerated approval pathway. Any regulatory approval based on robust amyloid lowering, improvement in other AD biomarkers, and safety would still involve the subsequent qualification of appropriate candidates for treatment by physicians knowledgeable about AD before any prescriptions are issued, and it would entail careful clinical follow-up.

In our view, amyloid lowering in secondary prevention trials of individuals who have amyloid plaques in the brain but are asymptomatic (as well as eventually forestalling amyloid plaque accumulation through primary prevention trials) should be accepted as compelling biomarker evidence of a drug-induced change in the fundamental biology of AD, providing the basis for regulatory approval and clinical follow-up. Moreover, the urgent need to provide more and earlier treatment to millions of mildly symptomatic AD patients suggests that the time is rapidly approaching to allow AD to join other progressive, devastating diseases for which traditional regulatory approval can be based on significant changes in a mechanistically linked and biologically meaningful biomarker coupled with reasonable safety data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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