The Future of Anti-Amyloid Trials

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Abstract

The termination of many clinical trials of amyloid-targeting therapies for the treatment of Alzheimer’s disease (AD) has had a major impact on the AD clinical research enterprise. However, positive signals in recent studies have reinvigorated support for the amyloid hypothesis and amyloid-targeting strategies. In December 2019, the EU-US Clinical Trials on Alzheimer’s Disease (CTAD) Task Force met to share learnings from these studies in order to inform future trials and promote the development of effective AD treatments. Critical factors that have emerged in studies of amyloid monoclonal antibody therapies include developing a better understanding of the specific amyloid species targeted by different antibodies, advancing our insight into the mechanism by which those antibodies may reduce pathology, implementing more comprehensive repertoires of biomarkers into trials, and identifying appropriate doses. Studies suggest that Amyloid-Related Imaging Abnormalities – effusion type (ARIA-E) are a manageable safety concern and that caution should be exercised before terminating studies based on interim analyses. The Task Force concluded that opportunities for developing effective treatments include developing new biomarkers, intervening in early stages of disease, and use of combination therapies.

Key words: Alzheimer’s disease, dementia, amyloid hypothesis, monoclonal antibody treatment, BACE inhibitors, combination therapy.

Introduction

Despite encouraging results from the aducanumab Phase 1 and BAN2401 Phase 2 anti-amyloid antibody clinical trials, amyloid-beta protein (Aβ)-based strategies for the treatment of Alzheimer’s disease (AD) appeared to take a crippling blow in March 2019 when Biogen announced it was terminating two clinical trials (EMERGE and ENGAGE) of the anti-Aβ monoclonal antibody aducanumab based on the results of an interim analysis demonstrating a lack of benefit or ‘futility.’ The field had another major challenge in July when Novartis, Amgen, and the Banner Alzheimer’s Institute announced termination of pivotal trials of the beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitor umibecestat after an interim analysis identified cognitive worsening in trial participants. This marked the fifth failed BACE inhibitor in less than two years, two with trials stopped because of adverse events (Merck’s verubecestat and Janssen’s atabecestat) and two trials stopped for lack of efficacy (Astra Zeneca and Eli Lilly’s lanabecestat and Eli Lilly’s LY3202626) (1–3). A fifth BACE inhibitor trial of Eisai and Biogen’s elenbecestat was halted in September 2019 due to an unfavorable risk/benefit profile (4). Trials for another anti-Aβ monoclonal antibody, Genentech and Roche’s crenezumab, were terminated in 2019 for futility (5).

Then, in October, a stunning reversal: Biogen
announced that the futility analysis in the aducanumab trial was misleading. Analysis of a larger data set indicated that aducanumab did indeed slow cognitive decline in trial participants who received a higher dose of the drug for longer periods of time in one of the two studies. Following this announcement, Biogen indicated they planned to submit aducanumab to the U.S. Food and Drug Administration (FDA) for regulatory approval. Any form of approval for aducanumab has the potential to transform the AD field, providing hope for patients and researchers alike. Regulatory success could also reinvigorate support for the amyloid cascade hypothesis, which posits that deposition of Aβ in the brain leads to the neurodegeneration and dementia that characterize AD. This hypothesis has driven the development of AD therapeutics for decades. Secretase inhibitors block production of Aβ, while anti-Aβ antibodies are designed to clear Aβ and prevent the formation of amyloid plaques as well as neutralize soluble Aβ oligomers. Prior to the announcement of aducanumab’s potential beneficial effects, no secretase inhibitor and only two monoclonal antibodies --- BAN2401 and gantenerumab --- had preliminary evidence of possible efficacy against Aβ, and there was much speculation in the field that the amyloid hypothesis was dead or at least unhelpful in guiding development of AD therapeutics. However substantial emerging evidence supports the amyloid cascade hypothesis (6).

To better understand the implications of these clinical trial results and the future of amyloid-based therapies, the European Union and United States Clinical Trials on Alzheimer’s Disease Task Force (EU/US CTAD-TF) convened a meeting in San Diego on December 4, 2019, bringing together industry scientists involved in clinical trials of anti- Aβ and other AD therapies along with representatives from pharmaceutical, biotechnology, diagnostics, and medical device companies, academic researchers, clinicians, and non-profit organizations. Their goal was to articulate lessons learned from these trials with the hope of enabling future successful trials that will lead to the approval of effective treatments for AD.

Learnings from trials of anti-amyloid monoclonal antibody trials

The Task Force discussed five anti-amyloid monoclonal antibody therapies currently in clinical development: aducanumab (7), BAN2401 (6), gantenerumab (8), solanezumab (9–13), and donanemab. Other anti-amyloid monoclonal antibodies (e.g., crenezumab) are also in development (5, 14). As summarized in Table 1, these antibodies target different forms of amyloid, may have different mechanisms of action, and are being tested for efficacy at different stages of disease.

The importance of dose

The futility analysis in the ENGAGE and EMERGE aducanumab trials -- two identically designed Phase 3 studies -- was based on a pooled interim dataset of approximately 50% of enrolled participants using a probability calculation that assumed non-heterogeneity between the two studies. A subsequent analysis of a larger dataset, however, revealed that protocol amendments allowing increased dosing in apolipoprotein E epsilon 4 (APOE4) carriers had differential effects on the two studies due to the relative timing of enrollment. This analysis demonstrated a statistically significant reduction in clinical decline across multiple clinical endpoints among early AD patients in EMERGE, likely due to high dose exposure to the drug. Participants in the ENGAGE trial who had received higher doses (10 mg/kg) for at least 10 doses had clinical effects similar to those of the EMERGE participants. Amyloid positron emission tomography (PET) studies demonstrated dose-dependent reduction of brain amyloid deposition across both trials.

Other trials have also demonstrated substantial dose-related amyloid lowering. Study 201 of BAN2401 used an adaptive randomization design with six arms to understand the impact of dose and minimize the number of participants treated with ineffective doses. The highest dose (10 mg/kg biweekly) produced the greatest slowing of disease progression and most robust reduction in brain amyloid levels compared to placebo and is used in the recently-launched Phase 3 Clarity AD study.

Open-label extensions of two early Phase 3 gantenerumab trials, in which study participants were assigned one of five titration schemes, also showed that five times higher dose of gantenerumab than was used in the earlier phase 3 studies drove increased amyloid reduction assessed with amyloid PET imaging (15). These findings prompted the initiation of a new Phase 3 program using this five-fold higher doses.

Mechanism matters

Amyloid is not a monolithic target but a family of monomers, oligomers, protofibrils, and fibrils; and different anti-Aβ antibodies target partially different species. The molecular dynamics by which targeting different species results in variable effects on plaque burden and brain volume loss are not well understood; however, these differential mechanisms may help explain the different trial effects observed. Solanezumab was hypothesized to remove brain amyloid through what is called the “peripheral sink hypothesis,” i.e., by increasing the clearance of soluble Aβ via the formation of antibody-Aβ complexes in the plasma. However, pharmacodynamic studies showed that a reduction of Aβ in the peripheral compartment failed to shift the equilibrium between Aβ species enough...
**Table 1. Anti-amyloid monoclonal antibody therapies**

| Drug Name (Sponsor) | Amyloid species targeted | Putative mechanism of action | Clinical trials | Status of development | References |
|---------------------|--------------------------|-----------------------------|-----------------|-----------------------|-----------|
| Aducanumab (Biogen) | Aggregated Aβ | EMERGE and ENGAGE (Phase 3) MCI due to AD and mild AD dementia with positive amyloid PET scan 2/3 of participants ApoE4 carriers | EMERGE and ENGAGE (Phase 3) Biodata analysis showed no significant reduction in cognitive decline Biomarkers: CSF pTau and total Tau reduced Decreased SUVR on amyloid PET | Terminated March 2019 based on futility analysis Further analysis showed reduced cognitive decline at high dose Plan to submit regulatory filing | Sevigny 2016 |
| Gantenerumab (Roche) | Aβ fibrils, oligomers, aggregated Aβ | SCarlet RoAD (Phase 3) MCI due to AD with CSF evidence of amyloid pathology MARQUERITE RoAD (Phase 3) MILD dementia due to AD with CSF evidence of amyloid pathology GRADUATE 1 and 2 (Phase 3) MCI due to AD and mild AD dementia with evidence of amyloid pathology by CSF or amyloid PET scan | Biomarkers: decreased SUVR on amyloid PET scans | Terminated with SCarlet RoAD Open-label extension with titration to higher dose | Ostrowski 2017 |
| Crenezumab (Roche) | Aβ monomers, oligomers | ABBY (Phase 2) in mild-to-moderate AD BLAZE (Phase 2) biomarker study CREAD 1 and 2 Prodromal to mild AD API study in Autosomal Dominant AD | Biomarkers: no effect on hippocampal, ventricular, or whole brain volume; increased CSF Aβ42 | Failed to meet primary and secondary endpoints. | Cummings 2018 |
| Solanezumab (Eli Lilly) | Soluble, monomeric Aβ | EXPEDITION 1 and 2 (Phase 3) — mild to moderate AD EXPEDITION 3 (Phase 3) — clinical diagnosis of mild dementia due to AD plus evidence of amyloid pathology DJAN-TU Study in Dominantly Inherited AD Anti-Amyloid treatment of Asymptomatic Alzheimer’s Disease (A4) | Primary endpoint not met. | Active study, not recruiting. | Farlow 2012, Doody 2014, Siemers 2016, Honig 2018, Schwarz 2019, |
| BAN 2401 (Eisai) | Soluble and insoluble Aβ aggregates | Study 201 (Phase 2) - MCI due to AD or mild AD. Adaptive randomization Clarity AD (Phase 3) - MCI due to AD or early AD with amyloid pathology AHEAD 3-45 in Predicinal AD with intermediate (A3) and elevated (A4S) amyloid | Slowing of cognitive decline Biomarkers: multiple ATN biomarkers (pTau, total tau, neurogranin, NfL) moved in expected direction. | Open-label extension | van Dyck 2018 |
| Donanemab (Eli Lilly) | Pyroglutamate forms of Aβ found in amyloid plaques | TRAILBLAZER (Phase 2) in combination with BACE inhibitor | TRAILBLAZER (Phase 2) in combination with BACE inhibitor | BACEi arm of trial discontinued | |
to cause a substantial reduction of fibrillary Aβ in the brain (16); the possible beneficial effect of solanezumab on cognitive decline may nonetheless be mediated by its binding to smaller, diffusible forms. Other possible mechanisms of anti-Aβ antibodies include direct targeting of Aβ plaques or other toxic species of Aβ for removal or activating phagocytosis of Aβ by microglia (17). Clinical trials of solanezumab in mild-moderate AD and in prodromal/mild AD failed to show a drug-placebo difference and no effects on biomarkers were observed. Solanezumab continues in the Anti-Amyloid treatment of Asymptomatic Alzheimer’s disease (A4) study of cognitively asymptomatic participants with positive amyloid imaging.

The effects of anti-Aβ antibodies on brain volume loss is poorly understood. In the EXPEDITION trials, treatment with solanezumab showed a modest but statistically insignificant slowing of brain atrophy (13). Gantenerumab produced no such effects on the measures collected (8). One theory suggests that driving down amyloid may itself be reflected as a reduction in brain volume. The effects on brain volume, however, could differ depending on which form of amyloid the antibody targets (e.g. plaques versus oligomeric forms). Further analysis of data from anti-Aβ antibody trials may help clarify this issue. The correlation of treatment-related brain volume loss and disease progression is also unclear.

**ARIA appears to be a manageable safety concern**

The incidence of amyloid-related imaging abnormalities – effusion type (ARIA-E) associated with anti-Aβ antibody treatment has been a substantial concern in the development of these therapies (18). For example, in the aducanumab trials, ARIA-E was seen in more than one-third of participants, although these episodes were typically asymptomatic and resolved within 4-16 weeks without long-term sequelae. ARIA-E was also observed in about 10% of participants in the BAN2401 Phase 2 study, occurring primarily in the first three months of treatment.

Recent studies suggest that ARIA-E can be safely managed by titrating drug to the target dose. For example, in the gantenerumab studies, titrating to the target dose reduced ARIA-E incidence in both APOE4 carriers and non-carriers and the majority of episodes were asymptomatic. Other studies have suggested that APOE4 carriers are at higher risk for ARIA-E. While ARIA-E appears to be manageable, uncertainty remains about whether even a minimal risk could be problematic for preclinical AD patients, or whether ARIA-E occurs more frequently in earlier stages of disease or in individuals with lower levels of vascular amyloid.

Although it may be challenging, it will be necessary to develop criteria that could be used in primary care settings for safely beginning treatment and monitoring for ARIA-E should an anti-Aβ monoclonal antibody treatment be approved for AD. A better understanding of the mechanisms involved could relieve concerns among primary care physicians once these therapies become available.

**Interim and futility analyses are useful only if appropriately designed**

Futility analyses are designed to protect participants from unnecessary exposure to drugs that have little chance of providing benefits, but if they result in premature termination of a trial, participants and sponsors alike – indeed, the entire field – may suffer adverse consequences from a failure to identify efficacious treatments and the failure to collect a complete dataset from the trial (19). The aducanumab Phase 3 program is not the only example in the field in which interim analysis wrongly predicted futility, raising questions about the design and appropriateness of futility analyses.

Among the fundamental tenets of futility analyses is that participants included in the analysis are representative of those in the full dataset and that drop-outs are equally distributed across all treatment groups. Protocol amendments made in the course of the aducanumab study, however, resulted in non-identical interim and final populations and in cohorts that had received different doses for different periods of time.

All futility analyses come with a price: loss of statistical power to demonstrate efficacy. This cost must be carefully weighed against any benefits from early termination. While there are clear advantages to stopping early when failure is inevitable, the possibility of misleading futility analyses suggests that criteria for defining failure versus success need to be very carefully specified. To implement criteria for interim analyses requires a better understanding of the clinical-biological trajectories of disease progression in stratified patient populations (19, 20). Interim analyses could also benefit from looking at the totality of evidence and by aggregating signals to reduce noise.

**Responder analyses could help identify subgroup differences**

To determine the disease stage at which a treatment may be efficacious, the optimal duration of treatment, and other patient characteristics that may affect efficacy, responder analyses of trial data and data from open-label extension studies can be valuable. Post-hoc exploratory data analyses may yield improved understanding of study results and inform the design of future studies. For example, in the SCarlet RoAD study of gantenerumab, an exploratory analysis that classified participants according to whether they were slow or fast progressors suggested...
that fast progressors showed a greater exposure-dependent slowing of clinical and cognitive decline with treatment (8). While not a classic responder analysis, the exploration of the faster progressing subset allowed modeling related to a drug-placebo difference and helped to define inclusion criteria for the ongoing Phase 3 GRADUATE program with higher dose of gantenerumab.

Moving forward with amyloid-based therapies

Genetic, neuropathologic, biochemical, and now clinical trials support the amyloid hypothesis of AD while recognizing that downstream pathological processes contribute importantly to the development of the disease (6). Many questions remain to be answered in order to translate the amyloid hypothesis into efficacious therapies. For example, further research is needed to determine which Aβ species are most important to target, whether relevant Aβ species change over the course of disease, if there is an optimal time for targeting a particular Aβ species, and whether at some point amyloid becomes less relevant or irrelevant. Developing a larger repertoire of biomarkers to predict disease onset and progression, e.g. microglial activation biomarkers, may help clarify the role of amyloid-related mechanisms as well as other mechanisms in disease progression (21). Preliminary data from the monoclonal antibody trials suggest there are “downstream” effects on cerebrospinal fluid levels of neurofilament light, neurogranin, and tau. These may be crucial measures of the biological effects of interventions and that can eventually be compared across trials.

An effective treatment may also require an Aβ-targeting drug in combination with a drug targeting another mechanism (e.g. neuroinflammation) or two drugs that target different amyloid mechanisms (e.g. production and clearance of Aβ) (22). Investigators have explored targeting Aβ in combination with tau, the protein found in the neurofibrillary tangles that along with amyloid plaques represent the major pathological hallmarks of AD. Moving this approach forward, however, will require a better understanding of the value of various tau-related targets, the relationship of amyloid to the level of tau burden as well as the time lag between amyloid deposition, tau deposition, and cognitive impairment (23). Employing tau PET studies in clinical trials may help define these aspects of the role of tau in AD (24,25). Other tau biomarkers are in development. For example, Walsh and colleagues have shown that an N-terminal fragment of tau (NT1) and p-tau in plasma are significantly increased in AD and mild cognitive impairment (MCI) (26).

Analysis of data from several failed clinical trials of amyloid-targeting drugs suggest that to slow or prevent disease progression, it may be necessary to intervene at very early, pre-symptomatic stages of the disease (27,28). Studies currently underway to test this include the A4 study in clinically normal older individuals with elevated amyloid levels on screening PET; and the AHEAD 3-45 study in clinically normal individuals with elevated or intermediate amyloid. Other prevention trials are underway in clinically normal participants at increased genetic risk of developing AD, including the Alzheimer’s Prevention Initiative (API) Colombia Trial (20). The DIAN-TU studies involving both clinically normal and symptomatic autosomal dominant mutation carriers recently reported negative topline results. The challenges inherent in these prevention trials include the difficulty of detecting a slowing of progression in cognitively normal individuals and the resulting large sample size and long trial durations required; the hope of preventing AD has motivated many individuals around the world to volunteer for these studies.

Very early intervention, including primary prevention, may be more feasible with active vaccination or oral therapy rather than passive immunotherapy requiring repeated intravenous or subcutaneous administration. Active vaccination against Aβ remains a plausible strategy (e.g. CAD-106; UB-311). Orally bioavailable BACE inhibitor programs have been halted with concern about observations of cognitive worsening in trials; however, evidence that this cognitive toxicity is dose-related and reversible raises hope that viable regimens may eventually move forward.

Conclusions

The termination of multiple clinical trials for futility or adverse events has had a major impact on the AD clinical research enterprise. However, evidence strongly supports amyloid as a viable target although not the only important target. Given the complexity of AD pathology, combination treatment will likely be needed. If antibody trials are sufficiently positive, they could represent a good first step towards combination treatment and lead to financial coverage and use of amyloid PET, which would be a major advance for the clinical care of AD.

To optimize the potential benefits and reduce the potential risks to participants as much as possible, methodological improvements in the design and conduct of clinical trials are needed. For example, adaptive dose finding studies may result in more patients assigned to an effective dose and avoid exposure of patients to ineffective doses. In addition, since disease modification depends on protecting neurons from the pathology, a better understanding of neuroprotection, the relationship of the biological underpinnings of the aging process (30), and the development of intermediate biomarkers of neuroprotection are needed. Advancing understanding of the complexity underlying the development of AD and potential interventions that could slow or halt the disease pathophysiological progression will require more discovery science as well as increased use of platform trials. Public-private partnerships with strong
collaborations and data sharing will be necessary to accelerate these efforts, along with broad public engagement.

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