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Aducanumab and the "post-amyloid" era of Alzheimer research?

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The controversial approval of the anti-amyloid therapy aducanumab for treatment of Alzheimer disease (AD) is changing the face of dementia care and research. The advent of clinically available anti-plaque drugs will shift both basic and clinical research priorities and create a new set of questions, challenges, and opportunities for AD researchers.

A brief history of anti-amyloid antibody therapies

Blocq and Marinesco first described the senile plaque in 1892, while Alois Alzheimer was the first to link plaques and tangles to progressive dementia nearly 15 years later. However, the molecular characterization of amyloid did not occur for nearly 8 decades until Amyloid-beta (Aβ) was first isolated from blood vessels (termed amyloid angiopathy) in 1984 by Glenner and Wong. Subsequently, mutations in three genes involved in the production or aggregation of the Aβ protein were found to cause an autosomal-dominant form of early-onset AD which shares many cardinal clinical and neuropathological features with the far more common sporadic AD (Tanzi et al., 1991). Thus commenced the 35-plus-year march toward a potential disease-modifying agent targeting brain amyloid as a therapeutic for AD. However, early anti-amyloid therapies all failed in phase III clinical trials. These included the anti-Aβ monoclonal antibodies bapineuzimab, solenezumab, and crenezumab, all of which failed to meet primary endpoints regarding the slowing of cognitive decline in patients with mild to moderate AD dementia. Overall, more than 10 different anti-amyloid agents have failed in large phase III trials, while dozens more have failed in smaller trials. These are several potential explanations for these failures. One is the drugs themselves, because none of these early agents showed the ability to effectively remove amyloid plaques, and several had deleterious off-target effects. Another is trial design, because these studies enrolled patients without evidence of amyloid pathology and targeted patients with more advanced symptomatic AD, which is perhaps too late for intervention. Finally, these failures could suggest that amyloid is not an ideal therapeutic target for symptomatic AD.

Over the past two decades, neuropathologic and biomarker studies revealed that AD pathology was common in the brains of persons without cognitive impairment (Bennett et al., 2006). The discovery of positron emission tomography (PET) tracers and cerebrospinal fluid markers for brain amyloid set the stage for presymptomatic trials of persons at risk for or with brain amyloid in the absence of clinical symptoms (Morris et al., 2009). The final piece was to reframe AD as a neuropathologic disease which begins as preclinical AD, thereby allowing space for pharmaceutical companies to intervene in persons without cognitive impairment (Jack et al., 2018). While we do not yet have data on preclinical anti-amyloid therapy for AD, this knowledge has focused therapeutic trials on the earliest stages of symptomatic AD.

In 2016, Biogen reported data from the phase 1b (dose escalation) PRIME trial for its newest anti-amyloid antibody, aducanumab (Sevigny et al., 2016). They observed a dose-dependent reduction in brain amyloid burden by amyloid PET imaging. Further, clinical data from a small cohort of patients suggested a slowing of cognitive decline among those receiving the highest dose of the drug. This was a striking finding, as no drug in this class had ever been shown to lower amyloid burden and impart a clinical effect. Unlike other monoclonal antibodies synthesized in a laboratory, aducanumab is an endogenous human antibody which binds to Aβ oligomers and plaques rather than monomeric Aβ. It appears to engage its target *in vivo* and to be a potent amyloid-removing agent. Notably, Biogen enrolled patients in PRIME with positive amyloid PET scans, ensuring that they actually had amyloid deposits, and restricted the trial to those with very mild AD symptoms.

Biogen carried this strategy forward into two large phase III trials, ENGAGE and EMERGE, needed to seek regulatory approval. A tumultuous series of events ensued. First, both trials were stopped early due to planned futility analyses. Futility analyses are frequently employed to stop a trial that will not meet its primary end point in order to save time and money. After the trials were stopped, no new patients were enrolled, but those who were already randomized were allowed to complete their scheduled visits and continue therapy. Then, uncharacteristically, Biogen announced months later that further analysis had revealed a positive signal in one of the two trials. Armed with new analyses and additional data from the study close-out phase, Biogen announced that they were seeking regulatory approval from the FDA. They claimed that EMERGE was a success; patients receiving the highest drug dose (10mg/kg) demonstrated a significant reduction in amyloid burden and met the primary endpoint of clinical efficacy with a modest slowing of cognitive decline (22% based on the Clinical Dementia Rating Sum Boxes) (Haeberlein et al., 2019). However,

ENGAGE also showed a significant reduction in amyloid burden but did not provide evidence of cognitive slowing. A post hoc analysis of ENGAGE data examining only patients receiving the highest dose of therapy for at least 14 months revealed similar efficacy as was seen in EMERGE, though the number of patients was small (Haeberlein et al., 2019).

The FDA, despite internal disagreement and against the advice of its Advisory Panel, approved aducanumab for the treatment of AD, but not through the standard mechanism. Recognizing the conflicting clinical efficacy data, they granted the drug accelerated approval based on the drug's ability to lower amyloid burden, saying that this was "reasonably likely" to impart clinical improvement. Further, despite aducanumab having only been tested in patients with very mild, biomarker-proven AD, the FDA label initially gave no guidance on which AD patients could be treated with the drug, leaving this decision up to the Center for Medicare & Medicaid Services (CMS), insurance companies, and physicians. Public backlash to this broad indication prompted a revised label which narrowed the use to those with mild cognitive impairment or very mild AD but did not provide specific criteria.

Notably, aducanumab had common and significant side effects. In particular, amyloid related imaging abnormalities (ARIA), which are common in the entire class of drugs. ARIA range from vasogenic edema (swelling) of the brain to microbleeds. More than 40% of subjects on the drug experienced ARIA, and 7.5% were symptomatic (Haeberlein et al., 2019). However, no severe adverse events occurred. Thus, ARIA must be monitored with repeated MRI, and individuals with evidence of microbleeds at baseline, which indicates possible amyloid angiopathy, are likely excluded from therapy. Finally, the drug is administered as monthly infusions. Thus, in addition to the current estimated cost of $56,000 per year for the drug, there are a variety of other clinical expenses. Cost and side effects are not sufficient reasons to abandon effective pharmacotherapies, but debates will rage regarding the risk/cost versus benefit of this drug. To be clear, AD is a killer. Not in weeks or months, but it is in years. There is no market for T-shirts emblazoned with "I survived Alzheimer's disease!" The history of drug development for deadly diseases, in particular cancer therapy, is riddled with expensive interventions of unknown or dubious benefit at the time. Accordingly, considerable expense and risk must be expected with the early treatments of AD in the hope of less cost and risk on the other side.

Both Biogen and the FDA were applauded in some corners of the scientific community and vilified in others. But scientists are not policy makers. We generate the data, and policy makers are free to take other considerations into account. This approval also has the potential to change the landscape of AD drug development, as the FDA was previously unwilling to consider surrogate endpoints such as amyloid lowering for AD drugs, insisting on evidence of clinical efficacy. Several other anti-amyloid antibodies in development, including lecanemab and donanemab, have also shown efficacy in lowering amyloid and some indication of slowing clinical decline in smaller phase II studies (Mintun et al., 2021; Swanson et al., 2021). These agents have already been given "breakthrough" designation by the FDA, and they and several others are now positioned to pursue accelerated approval in the same manner as aducanumab. Meanwhile, Biogen has nine years to demonstrate clinical efficacy of aducanumab through a phase IV (post-marketing) trial. Regulatory agencies, insurers, healthcare systems, and physicians are scrambling to develop infrastructure and policies to appropriately provide aducanumab to patients. Experts are grappling with a dizzying array of critical clinical questions regarding appropriate patient selection, safety, treatment duration, and response monitoring. A few medical centers have pointedly refused to treat patients with the drug, while some private insurers and the Veteran Affairs system have balked at paying for it, with both groups citing lack of clinical efficacy. CMS is weighing its coverage plan and criteria, which will influence coverage in general. Meanwhile, the FDA has called for an investigation into its own approval processes for aducanumab.

Implications for basic AD research

What is clear for now is that there is an FDA-approved drug that can lower amyloid in the human brain, with additional agents in late development and watching the regulatory agency carefully. So, has the field entered the "post-amyloid" era of AD research? The answer is no. It is unclear if aducanumab affects the slope of cognitive decline in symptomatic patients in a clinically meaningful way, so improvements, either in the drug itself or how it is used, are needed. Future anti-amyloid drugs will certainly be cheaper, safer, and easier to use than aducanumab, so further research in this area is still warranted. Many important basic amyloid-related research questions remain unanswered: Why does amyloid accumulate in some people in the first place? What mechanisms link aging to accumulation of amyloid? What interventions in middle age might prevent this process entirely? Studies of the impact of earlier-life factors, such as metabolic disorders, vascular disease, sleep/circadian function, exercise, cognitive enrichment, stress, immune/infectious factors, and microbiome alterations on the development of AD pathology (including amyloid) hold promise for the development of primary prevention strategies.

While it is still unknown if prevention of initial amyloid deposition can prevent AD, clinical trial data clearly demonstrates that after some point in the disease process, the removal of amyloid becomes ineffective, and degeneration progresses in an amyloid-independent manner. If we accept the assumption that amyloid is an initial instigator of a downstream, autonomous degenerative process, likely involving tau aggregation and neuroinflammation, then understanding the exact mechanisms by which amyloid ignites this cascade is among the most critical questions. Newer mouse models which develop both amyloid and tau pathology, or involve tau seeding of amyloid plaques (He et al., 2018), may aid in understanding the interaction between plaques and other degenerative proteinopathies. Therapeutic strategies targeting co-existent proteopathies such tau, alpha-synuclein, or TDP-43, or that generally augment cellular capacity to degrade or clear protein aggregates, may gain efficacy when paired with plaque removal. An enhanced knowledge of the blood-brain barrier and vasculature in AD could help augment antibody penetration into the brain and

could be used to mitigate ARIA. The explosion of studies on brain immune responses to amyloid is beginning to reveal critical roles for glial cells, as well as the adaptive immune system, in the propagation of tau spreading in the setting of amyloid pathology and in amyloid and tau-mediated neuronal injury. Ultimately, if immune cells serve as a critical link between amyloid plaques and downstream neurodegeneration, then immunomodulatory therapies might be effectively paired with anti-plaque antibodies in early AD patients. Thus, while effective plaque-removing antibodies may shift research priorities away from amyloid pathology a bit, there are still many important unanswered questions related to amyloid that have high clinical relevance.

Future directions for dementia

The last question is whether we should even be targeting amyloid in AD in the first place, or if other targets offer more potential. If one assumes that amyloid is responsible for initiating all of the downstream tau pathology, then classic AD accounts for about a third of age-related cognitive decline (Boyle et al., 2018). Of course, as noted above, the removal of amyloid once the cascade is initiated may be of little to no value. Other common brain pathologies, most beyond the resolving power of current methods in living humans, account for another third. In fact, the majority of people with AD dementia have two or more brain pathologies (Boyle et al., 2019). Finally, extant brain pathologies leave a third of Alzheimer's dementia unexplained. Much of this may be explained by resilience, i.e., genes and proteins associated with faster or slower cognitive decline that are unexplained by brain pathologies. All human physiologic systems have factors that maintain or degrade their functional capacity over time (Yu et al., 2020). There is no evolutionary pressure to build systems to maintain cognition in response to age-related brain pathologies. Whatever systems are there were honed long before most people routinely lived into their seventies and eighties. Just as the immune system has only a few mechanisms capable of responding to novel threats never experienced in human history (such as HIV, Ebola, Zika, and SARS), there are likely only a few brain resilience systems capable of responding to age-related diseases not experienced throughout most of human history. If such systems in the brain were druggable, we could offset, in part, the consequences of any combination of age-related pathologies without the need for an array of biomarkers or pathology-specific therapies.

Conclusions

With aducanumab, we now have a drug which can remove amyloid plaques from the human brain. When applied to patients with mild AD dementia, this intervention has questionable clinical efficacy. This drug does not cure AD, nor does it prove or disprove the amyloid hypothesis. Instead, it provides a new potential weapon against AD that we must understand and learn to use effectively, if possible, and that can potentially be paired with other therapies. The limitations of this therapy also illustrate the need for continued research into amyloid-dependent and independent mechanisms in AD.

DECLARATION OF INTERESTS

Dr. Musiek has provided consultation and has received research funding from Eisai Pharmaceuticals, the co-developer of aducanumab and developer of lecanemab. This interaction with Eisai is related to basic sleep research and is unrelated to aducanumab, lecanemab, or any other amyloid antibodies. No personal compensation was provided. Dr. Bennett has consulted for Takeda, Abbvie, Origent, and Vigorous Minds. He has received research funding from Biogen, the developer of aducanumab, for data analysis of data generated from his own group, and from Neurovision.

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