Commentary

Beyond Aducanumab and the Amyloid Hypothesis

Wei Cao[1*]

[1]Department of Human and Molecular Genetics, Baylor College of Medicine, USA

***Corresponding author**: Wei Cao , Huffington Center on Aging, Department of Human and Molecular Genetics, Baylor College of Medicine, Houston, TX 77030, USA; E-mail: wei.cao@bcm.edu

Received: April 15, 2019; **Accepted**: May 02, 2019; **Published**: May 09, 2019

Citation: Cao W (2019) Beyond Aducanumab and the Amyloid Hypothesis. Front Neuroinflamm Neurodegener Dis 3(1): 100008.

Abstract

Alzheimer's disease (AD) represents the most predominant form of dementia. Currently, 5.8 million Americans are living with AD; and this number is projected to rise to 14 million in 2050. With only a handful of existing drugs to alleviate symptoms, sadly there is no disease modifying treatment option available for AD patients. The recent development of a closely watched AD drug trial has caught attention of patients, scientists, clinicians and drug developers. In this commentary, I'd like to briefly review the key findings of Aducanumab and discuss the broader implications on the guiding principles and strategies in AD therapeutic development.

Keywords: *Alzheimer's disease, Aducanumab, amyloid hypothesis, clinical trials, Amyloid beta, PRIME, ENGAGE, EMERGE*

Aducanumab: Mechanisms and Trials

Amyloid beta (Aβ) protein is prone to aggregate and makes up the deposited plaques, a defining pathology of AD. Aggregated Aβ, more so than the monomeric Aβ, can be readily recognized by the circulating antibodies produced by the human humoral immune system [1]. It was demonstrated that anti-aggregated Aβ antibody, while exist in abundance in young individuals, declines in cognitively normal seniors and diminishes further in AD patients [1]. Given the pathologic involvement of Aβ oligomers and plaques, these presumably protective antibodies were deemed valuable as targeted immunotherapy. Aducanumab, a human IgG1 monoclonal antibody, was cloned directly from a de-identified blood lymphocyte library collected from healthy elderly subjects with no signs of cognitive impairment and cognitively impaired elderly subjects with unusually slow cognitive decline [2].

In vitro, Aducanumab displays high affinity towards oligomeric and insoluble fibrillar $A\beta_{1-42}$, but not soluble $A\beta_{1-40}$. On AD brain tissue, Aducanumab selectively stains amyloid plaques [2]. *In vivo,* a murine chimeric version of Aducanumab traffics from the periphery to the brain and preferentially binds to the parenchymal Aβ. Chronic dosing of such antibody dose-dependently reduces amyloid load in AD mouse model Tg2576 mice [2].

In a Phase Ib double-blind multicenter clinical trial PRIME (ClinicalTrials.gov identifier NCT01677572), 165 patients with prodromal or mild AD were randomized and received IV infusion of placebo or one of 4 doses of Aducanumab for 12 months. Molecular positron emission tomography (PET) imaging with florbetapir was used to confirm Aβ pathology at the time of patient recruitment. Treatment with Aducanumab effectively removed brain Aβ plaques in a dose- and time-dependent manner, based on PET imaging [2]. In conjunction, a slowing of cognitive decline was tentatively suggested, although the trial was not powered to prove clinical endpoints. Adverse effect of ARIA-E was transient but increased with the dosing of Aducanumab.

Two large Phase 3 trials, ENGAGE (ClinicalTrials.gov Identifier NCT02477800) and EMERGE

(ClinicalTrials.gov Identifier NCT02484547), were conducted by Biogen and Eisai to demonstrate the clinical benefit of Aducanumab. A combined more than 3200 patients with mild cognitive impairment (MCI) due to Alzheimer's disease or mild AD were recruited worldwide and received placebo or one of 2 doses of Aducanumab. At 18th month, a futility analysis concluded that trials would not reach their primary endpoint, *i.e.* the slowing of cognitive decline. On March 21, 2019, both trials were terminated abruptly.

The failure of Aducanumab at the late stage development in spite the impressive Phase 1b results was a shock to patients, clinicians, and scientists alike. While we are waiting for the detailed analysis from the trial sponsors, several points are worthwhile discussing now. First, how reliable is PET imaging as a sole molecular readout of Aβ modification? Until the completion of an autopsy examination, the potential interference by plaque modifying agent with PET detection remains a concern at the technical level. Second, it is well known that Aβ deposition may begin two decades or more before clinically noticeable cognitive decline. Although precaution was taken in the trial design, but is it still too late to eliminate Aβ in the patients with MCI or mild AD? Should other molecules, such as tau, be targeted at this stage instead? Last, does the result formally discredit the amyloid hypothesis (see next section) and a new paradigm is needed to direct the translational effort from now on?

The Amyloid Hypothesis

Since Alois Alzheimer described the first index case in 1906, tremendous progress has been made in the diagnosis, pathophysiology, genetics, molecular and cellular biology of AD. Formulated originally in early 1990s, the amyloid hypothesis conceptualized numerous clinical and genetic research findings and assigned a pivotal role of Aβ, in the form of dyshomeostasis, in AD pathogenesis [3-6]. It coincides succinctly with several key observations: 1) a subset of AD patients, who have early disease onset, bear genetic mutations in familial forms, which include germline mutations in APP, PSEN1 or PSEN2 that invariably result in the increased Aβ42 production; 2) all AD brains accumulate senile plaques that are composed of aggregated Aβ; 3) although majority of AD cases (sporadic form) are late onset and lacking familial mutations, they share similar pathological features with familial AD. Since then, this influential hypothesis has guided a vast amount of studies in revealing the pathological events downstream of Aβ imbalance [7].

The amyloid hypothesis logically argues for a therapeutic strategy towards reducing the production of or removal of Aβ in AD. Unfortunately, agents targeting the enzymes involved in APP processing showed no clinical benefit so far [8]. Numerous immunotherapy efforts to selectively deplete Aβ molecule from the brain, either by active or passive immunization, failed to modify AD effectively [8]. In principle, Aducanumab offers an improved design over the earlier anti-Aβ trials in two key aspects: 1) pre-screening of patients with amyloid PET imaging to ensure target presence, and 2) selective targeting of aggregated Aβ, a form directly implicated in AD pathology. The disappointing Aducanumab failure calls for a re-examination of our basic understanding of AD pathogenesis.

Broaden the Horizon for AD

From diagnosis to treatments, the complexity of AD and the challenges it imposes cannot be overstated. To this day, most would agree that AD by no means should be considered a neural-centric disease. One major limitation of the amyloid hypothesis is the over-emphasis on the events initiated from the neurons. It is clear that sporadic AD is genetically distinct from the familial form. Large scale genetic surveys on late onset AD have identified many risk genes involved in other biological processes, beyond Aβ biogenesis [9-11]. The functionality of human brains can be profoundly impacted by multitude of factors, individually, sequentially, or simultaneously. In addition to increased protein aggregation, AD brains often display reduced protein degradation, defective blood-brain barrier (BBB) and vasculature, profound inflammatory response, diminished neurogenesis, disruption of sleep and circadian rhythm, and microbial infections, etc. [12-15] (Figure 1). In addition, peripheral and systemic changes can powerfully modify

the CNS pathology [16-18]. Hence, the debate continues whether Aβ functions as the primary initiator or a by-stander of other pathological processes, a condition may likely even vary between AD patients. Regardless the role of Aβ, it is time to expand the scale of research investigations by testing new hypothesis, developing new models, and identify new pathways and targets.

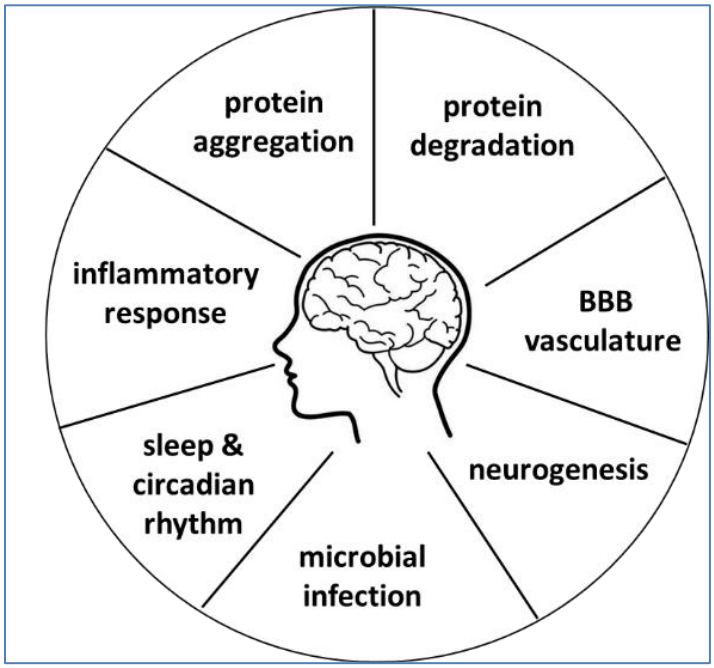

Figure 1: Multiple factors influence neurodegeneration

Next Generation AD Therapies

Our apprehension on the complexity of AD points to an urgent need to diversify the therapeutic approaches. Several early-stage developments target tau, a neuronal protein that pathologically interacts with Aβ and aggregates into neurofibrillary tangles, the latter is more proximate to neuronal dysfunction than plaques in AD [19,20]. Beyond Aβ and tau, significant number of AD brains also accumulate α-synuclein and TDP-43 aggregates, which are traditionally associated with Parkinson's disease and amyotrophic lateral sclerosis, respectively [21-23]. Given such intensity of mixed etiology, it is not difficult to foresee that targeting single misfolded protein species individually may not be sufficient to halt AD. On the flip side of the protein aggregates, boosting the brain's capacity to dispose protein waste by way of modifying the functions of proteasomes or autophago-lysosomes is another crucial avenue to tackle AD [24,25].

Neuroinflammation constitutes a key component of AD pathology [26,27]. Notably, a number of risk genes for sporadic AD exclusively operate in the immune system, esp. microglia, brain's resident immune cells [11,28,29]. However, it is clear by now that non-specific anti-inflammation drugs do not benefit AD patients [30-32]. Current neuroinflammation research aims to identify specific targets and pathways that are key drivers of inflammation, synapse loss, neurotoxicity and cognitive decline. Impressive progress in this area is being made and will facilitate the development of next generation of treatments.

On the other hand, lessening the risk of vascular disease has shown definitive beneficial effect on AD [33,34]. Healthy sleep-wake cycles may improve Aβ and tau dynamics and reduce the accumulation of these aggregates [35,36]. Life style changes in the form of exercise, dietary modification, and diabetes management, can significantly diminish the risk of AD [37,38].

Putting behind the frustration of the failed clinical trials, it is time to open one's mind and broaden the scope of our searches. Given the multifactorial nature of AD, an eventual combinational therapy may be essential for a successful disease modifying therapy.

Acknowledgments

The study was funded by NIH grant AG057587 and BrightFocus ADR A20183775.

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