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Commentary

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Disease Modification Therapy with Anti-Soluble Aβ Protofibril Antibody for Alzheimer Disease

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Commentary

The FDA approved a new drug: lecanemab (or BAN2401, brand name Leqembi, Biogen and Eisai) for treating Alzheimer's disease (AD) on January 6th, 2023, under the accelerated approval pathway. The approval was based on the results from a Phase 2 clinical trial and part of a Phase 3 trial (Clarity AD) showing a reasonable likelihood of clinical benefits [1, 2]. This approval is acclaimed as a breakthrough in treating patients with early AD because of its disease modifying effect.

AD is a progressively devastating neurodegenerative disorder presenting as cognitive decline, personality changes and dementia. In 2020, there were 5.8 million Americans suffering from AD. The incidence of AD is estimated at 0.4% in people aged 65 to 74 but the number likely doubles every 5 years in people 65 and older. Approximately 14 million people are estimated to live with AD by 2060 [3]. While the etiology for AD is not completely understood, the amyloid hypothesis is the central idea proposed to explain the development of AD.

Amyloid-beta protein (Aβ) is generated from amyloid precursor protein (APP) whose cleavage is enzymatically catalyzed by three secretases, namely alpha-, beta-, and gamma, into several small fragments with different biologic activities (Figure 1) [4, 5]. The soluble products of these cleavages include: (1) sAPPα due to the action of the alpha-secretase. sAPPα harbors a part of the Aβ sequence (amino acids 1-18); (2) sAPPβ due to the action of beta-secretase, which does not carry Aβ sequence; or (3) sAPPγ due to the action of the gamma-secretase which encompasses all of the Aβ sequence and is only seen in rodents (Figure 1) [4, 5]. Thus, Aβ is generated from APP by beta- and gamma-secretase and constitutes the core component of senile plaques. Robust evidence showed that sAPPα is a trophic factor having neurotrophic and neuroprotective activities [6-8]. A lack of sAPPα causes neuronal death [8-10] in cell culture and worsens human AD symptoms in clinical trials [11-14].

There are several drugs clinically available for AD treatment, including cholinesterase inhibitors [Donepezil (Aricept), Galantamine (Razadyne) and Rivastigmine (Exelon)] and NMDA receptor antagonist [Memantin (Namenda)], however, they are considered as palliative measures with no effects on disease progression. The effect of Aducanemab (Aduhelm), an anti β-Amyloid (Aβ) peptide antibody approved by the FDA on AD in 2021 remains controversial [5].

Aducanumab is a recombinant human IgG1 monoclonal antibody preferentially targeting the antigenic epitope of the amino acids 3-7 on the N-terminal region of Aβ peptide [15] which overlaps the epitope within the domain of sAPPα (Figure 1). Laboratory studies showed that interfering with sAPPα expression by antisense oligonucleotides [9] or antibodies [8] to sAPPα or expressing

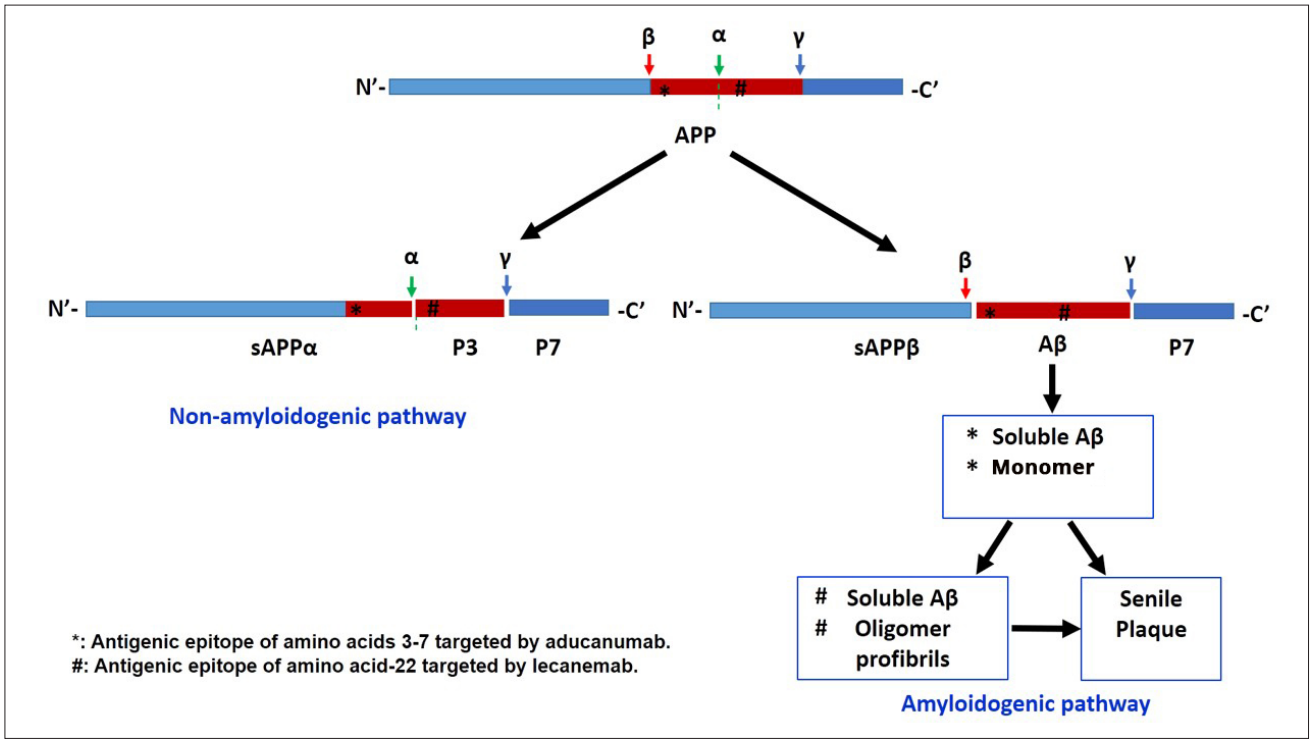

Figure 1: Processing of APP by secretases and amyloid antibody target sites.
In the non-amyloidogenic pathway, APP is cleaved by α- and γ-secretases leading to the genesis of sAPPα, p3 and P7.
In the amyloidogenic pathway, APP is cleaved by β- and γ-secretases leading to the formation of sAPPβ, Aβ and P7.
APP: Amyloid precursor protein; sAPPα: Soluble APP alpha; sAPPβ: Soluble APP beta; P7: AICD, APP intracellular domain.
*Antigenic epitope of amino acid s3-7 targeted by by Aducanumab .
#: Antigenic epitope of amino acid 22 targeted by lecanemab.

a truncated [10] sAPPs in cell culture caused neuronal death. Additionally, infusing a vaccine or antibody against part or the whole length of Aβ involving an epitope within the sAPPα domain worsened symptoms in patients with AD [11-14].

Lecanemab, the newly FDA-approved drug, is a genetically humanized IgG1 monoclonal antibody that preferentially targets soluble Aβ protofibrils. Protofibrils are intermediates in the Aβ aggregation process related to the proposed pathogenic role in AD [16]. Lecanemab does not bind to APP and only very weakly binds to monomers or fibrils of Aβ [17]. Notably, lecanemab was created from an mAb158 (IgG2a) [18] which was originally developed at Uppsala University, Sweden [16] based on the discovery of the Arctic mutation (p.E693G/p.E22G) in APP. Patients with this mutation developed typical phenotype of AD with high content of Aβ protofibrils and a relative scarcity of amyloid plaques [19]. The Arctic mutation occurs within the Aβ domain of the APP gene and causes an autosomal dominant phenotype of AD [20]. Notably, the Arctic mutation involves amino acid-22 of the Aβ peptide and is not present in the C-terminal domain of sAPPα. The C-terminal domain of sAPPα contains amino acids of 1-18 of the Aβ peptide. Therefore, lecanemab theoretically should not bind to, or interfere with sAPPα function (Figure 1) [17].

Early results of a Phase 3 randomized, controlled clinical trial (Clarity AD) confirmed lecanemab's clinical benefit [1, 2]. When given at 10 mg/kg biweekly, lecanemab produced positive results in patients with early AD on all primary and secondary outcomes compared to placebo. Clinical Dementia Rating-Sum of Boxes (CDR-SB) analysis was utilized to evaluate the severity of AD dementia and mild cognitive impairment (MCI) as the primary endpoint. CDR-SB scores were compared from baseline to 18 months showing 1.21 in the lecanemab-treated versus 1.66 in the placebo group, which Eisai claimed represents a 27% slowing of cognitive decline (p=0.00005). All the secondary measurements including the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog14), Alzheimer's Disease Composite Score (ADCOMS), and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for MCI (ADCS MCI-ADL) showed similar trends of a slowing of cognitive decline [21]. Brain amyloid was reduced by up to 93% and cognitive decline became delayed by 47% on the ADAS-Cog, and by 30% on the ADCOMS [21]. Notably, amyloid load became undetectable by positron-emission tomography (PET) in two-thirds of lecanemab-treated patients at 18 months. Additionally, evidence of significantly decreased tangle accumulation of tau in the medial temporal lobe evaluated by PET (with similar trends in other brain locations) was seen and the inflammatory biomarker GFAP for reactive astrocytosis was significantly reduced. Taken together, these findings suggest that lecanemab may be capable of modifying the progression of AD. Lecanemab is given 10 mg/kg biweekly for patients with mild AD or MCI [21]. The antibody can be detected in the CSF in a dose-dependent manner with half-life in serum elimination of seven days [22]. Eisai proposed that lecanemab will cost $26,500 per year for a person of average weight while ICER (the Institute for Clinical and Economic Review's health

benefit price benchmark) valued its cost-effectiveness ranging from $8,500 to $20,600 annually [23].

However, safety concerns remain. Lecanemab caused amyloid-related imaging abnormalities (ARIA) on MRI and its clinically associated symptoms although less frequent than those seen with Aducanemab [5]. ARIA-edema (ARIA-E) was 7.4-fold higher in lecanemab-treated patients (12.6%) vs the placebo group (1.7%). Approximately one-quarter became symptomatic although with transient and mild severity [21]. ARIA-hemorrhage (ARIA-H) was 6-fold higher in the lecanemab-treatment group (0.6%) vs the placebo group (0.1%). For patients on anticoagulants and lecanemab, the rate increased to 24-fold (2.4%) [21]. Furthermore, and not a trivial concern, ARIA-H was associated with 3 deaths from brain hemorrhage in the lecanemab open-label extension (Jan 2023 news).

Nevertheless, the approval of lecanemab will offer the opportunity to interrupt the course of the disease at the early stages, and may provide benefits to AD patients, their families, and caregivers. We are optimistically looking forward to seeing the mitigating effects of lecanemab on AD and validation in the extended open label phase 2 trial and the ongoing Phase 3 trial (Clarity AD).

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