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Opinion

Aducanumab, an FDA Approved Drug for Alzheimer's Disease

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Preface

Alzheimer's disease (AD) is an irreversible, progressive disease and most common cause of dementia that destroys memory and thinking skill, it remains a global health concern with ever aging population. Discovered by Alois Alzheimer's in 1906 [1], AD have been identified in 43.8 million people worldwide [2]. The pathological hallmarks of AD are intraneuronal neurofibrillary tangles (NFTs), extracellular deposits of amyloid-β (Aβ) peptides as ''senile'' β-amyloid plaques and decrease in neuronal cells.

Since the approval of Tacrine in 1993 by Food and Drug Administration (FDA), many drugs have been tested in preclinical animal models for AD treatment but failed to show efficacy in human clinical trials or are still waiting for approval under Phase I–III trials [3]. Additionally, all the available therapies only provide symptomatic relief. According to the Alzheimer's Association 2016 trajectory report, it was estimated that if by year 2025, a drug is available and is able to delay the onset of the disease, a total of 42% reduction in people suffering can be seen by year 2025 [4]. Aducanumab, an amyloid beta-directed antibody, is the first-of-its-kind drug recently approved by the USA (FDA) for AD treatment that target and affect underlying pathology of the disease with modest benefits on survival [5].

What is aducanumab

Aducanumab (a" due can' ue mab) (BIIB037) is a human immunoglobulin g1 (IgG1) monoclonal antibody selective for aggregated form of Aβ which is developed as therapy, a disease-modifying treatment for AD [6]. The rational towards its use is based upon the theory that neurological decline in AD is due to the accumulation of Aβ oligomers and fibrils formation which causes toxicity and ultimately leading to neuronal cell death (Figure 1).

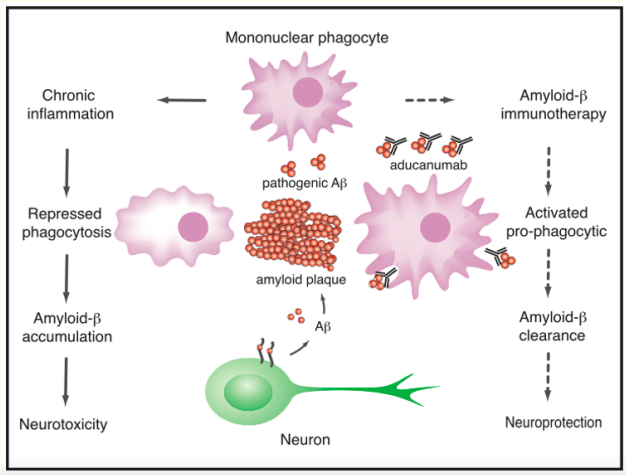

Figure 1: Targeting Mononuclear Phagocytes for Amyloid Clearance with Aβ Immunotherapy in response to aducanumab, mononuclear phagocytes (hematagenous macrophages or brain-resident microglia) home to and phagocytose pathogenic Aβ. In Alzheimer's disease (AD), brain mononuclear phagocytes have repressed phagocytosis, favoring Aβ accumulation and neurotoxicity (Image is adapted from [7] with permission granted by Immunity, Copyright 2016, Cell-press).

Neurimmune, a Zurich-based company, licensed the molecule aducanumab to Biogen in 2007. It first screening healthy elderly people with aducanumab for antibodies that could be protective. Neurimmune found that aducanumab was effective against fibrils, oligomers and decamers, the most toxic form, indicative aducanumab efficiency against disintegrating plaque and oligomers clean up. Additionally, it did not affect to soluble Aβ in the

vasculature [6]. Aducanumab is effective against mild cognitive impairment (MCI) patients of AD, who also has Aβ plaques buildup which can be confirmed via cerebrospinal fluid analysis or amyloid PET imaging diagnostic test. Although, no data is available for the effectiveness of the drug against early and late stages of AD.

Early competition

In year 2015, Alzheimer's Association International Conference in Washington, D.C., reported two high-profile, phase II trials of antibodies. One by the pharmaceutical company Eli Lilly, 'solanezumab' that slowed cognitive decline in 440 patients' trial of mild AD by 34% [8]. Whereas, the company Biogen, of Washington DC, showed that 'aducanumab' not only slowed cognitive decline at some doses but also lowered brain levels of Aβ, 27 people with mild AD who took a 10-mg dose showed significant cognitive benefits over controls, as well as reduced levels of Aβ in PET brain scans. Lilly launched a larger phase III trial of solanezumab in 2013, enrolling 2,100 people with mild symptoms and amyloid deposits in their brains. The study will end in October 2016. And last December, Biogen said that it would launch a phase III trial with 2,700 participants that would run for 18 months [9].

Another antibody 'bapineuzumab' a drug candidate of Pfizer's Wyeth unit, reduced the rate of Aβ plaque accumulation as evident from PET imaging, it also decreased the neurodegeneration biomarkers CSF tau and phospho-tau, however, showed no effect on CSF Aβ levels [10]. Whereas solanezumab showed no effect on plaque or phospho-tau levels, but had significant effects on CSF Aβ, leading to significant increase in levels of antibody-bound Aβ. These baseline biomarker changes were lenient for inclusion criteria, because 36% of ApoE4 non-carriers in the bapineuzumab trial had negative PET scans for Aβ. In contrast, the early phase study of aducanumab, had advantage because of its stringent inclusion criteria and it showed significant cognitive decline and Aβ plaque accumulation [8].

Phase 2 trial of 'Crenezumab' a mAb of Basel-based Roche company, that binds to different forms of Aβ (monomers, oligomers and fibrils) prove no efficacy mild-to-moderate AD, but it all supports amyloid as a treatment target and high-dose Crenezumab can be effective therefore a phase 3 trial was done [11].

Remark

Aducanumab a first-of-its-kind drug also come with side effects such as amyloid-related imaging abnormalities (ARIA), headache and allergic reaction. ARIA though do not cause any symptoms but can be serious as it is a temporary swelling in different area of brain, which further can sometimes cause dizziness, nausea and vision problems. In Europe, European Medicine Agency (EMA) has already recommended against the drug stating the lack of evidence of its efficiency and health safety concerns [12]. Also, the drug is approved under the accelerated approval pathway by the FDA, which means the drug will be provided early access to serious patients, where clinical benefit is expected in spite of uncertainty of side effects. Hence, the company requires to verify clinical benefit in a post-approval trial failure to do so will lead to withdrawal of the drug by FDA [5].

Drug name	Aducanumab
Trade name	Aduhelm®
CAS registry no.	1384260-65-4
Structure	Not available
Phase	Approved by FDA
Pharmacology description/ mechanism of action	Human monoclonal IgG1 antibody directed against amyloid β
Target patients	AD patients with mild cognitive impairment (MCI), who also has Aβ plaques buildup
Diagnostic tests	Cerebrospinal fluid analysis or amyloid PET imaging
Route of administration	Intravenous via 45-60-minute infusion every 4 weeks
Side effects	Amyloid-related imaging abnormalities (ARIA), headache, fall and allergic reaction
Estimated costs	Cost to patients is unknown. Biogen company has set a price of $56,000 per year

Table 1: Aducanumab drug summary.

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