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Research Progress of Alzheimer's Disease Monoclonal Antibodiesand Their Safety Assessments

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Abstract. This article focused on discussing two monoclonal antibodies (mAbs), lecanemab and aducanumab, which target at amyloid-beta protofibrils and fibrils as amyloid-beta plaques are considered as the key pathogenesis of Alzheimer's disease (AD). Detailed mechanism of AD including the formation of amyloid-beta plaques and tau protein was explained, as well as the efficacy, benefits and limitations of these two mAbs are discussed. Current studies shown that lecanemab and aducanumab have efficacy on reducing amyloid-beta plaques in AD patients. There are limitations to the usage of both lecanemab and aducanumab, such as the appearance of amyloid-relating imaging abnormalities (ARIA). However, findings suggested that less ARIA occurred in the administration of lecanemab, and to the most harmful kind of amyloid protein, lecanemab binds more tightly compared to aducanumab. Therefore, safety assessment of these two mAbs should also be considered. This article only focused on lecanemab and aducanumab, donanemab which was approved recently is not mentioned. It is worth pointing out that the appearance of lecanemab and aducanumab had revolutionized the treatment for AD, as this improve the life quality of AD patients. More effective mAbs and other treatments are still under investigations in order to lower the incidence, and provide more hope for curing AD.

Keywords: Alzheimer's Disease, monoclonal antibodies, lecanemab, aducanumab.

1. Introduction

A progressive neurological disorder that affects millions of individuals worldwide is AD. Memory loss, cognitive decline, and behavioral changes are main early indications and symptoms of AD. As of 2022, AD ranks as the seventh most common cause of death in the US. Data from Centers for Disease Control and Prevention indicate that AD usually first appears after age 65, and every five years after age of 65, the incidence of Alzheimer's disease doubles. While the precise aetiology of AD remains poorly known, aging, neuroinflammation, APOE-e4 allele, free radicals and other related lifestyle factors, such as cardiovascular diseases and diabetes are considered to elevate the risk of having AD [1].

Although the aetiology is complex and still remained uncleared, there are two existing mechanisms to explain AD, including the intracellular build-up of tau protein and the extracellular accumulation of amyloid-Aβ. These two substances are insoluble. Tau is the main component of neurofibrillary tangles, whereas Aβ is the main component of senile plaques. The deposition of Aβ is considered to be primary and unique to AD, and tau buildup is considered to be secondary and is observed in various degenerative disorders. It has also been discovered that Aβ is toxic to neurons, which resulting in synaptic damage, loss of long term potentiation, and eventually neuronal death. (M.D, n.d.). Neurodegeneration caused by the progressively death of neurons is the hallmark of AD. Neural degeneration typically initiates in the entorhinal cortex of the hippocampus region. Neurons in the neocortex and basal forebrain, especially cholinergic neurons, are being lost along with these degenerative alternations [1].

There are currently no cures for AD, treatments targeting at AD are limited but could slow the growth of the condition and momentarily relieve symptoms. However, the authorisation of anti-amyloid mAbs and their implementation into clinical treatment are transforming the field of AD therapy. The expedited authorisation method has resulted in the approval of two MABs: abucanumab (Aduhelm

®) and lecanemab (Leqembi ®). The US Food and Drug Administration (FDA) may standard approve lecanemab (Leqembi ®) based on clinically convincing results, while donanemab may be approved based on encouraging Phase 2 data. On amyloid positron emmision tomography (PET), amyloid has been shown to significantly decrease when treated with lecanemab and donanemab, as well as a decreasing rate of clinical reduction in clinical trails. In conclusion, this article is aimed at discussing mAbs targeting amyloid-Aβ and tau protein in an effort to improve AD patients' quality of life [2].

2. AD's Pathophysiology

The precise mechanism underlying AD is still unknown and complicated. However, neurofibrillary tangles (NFTs) and amyloid-beta (Aβ) plaques' production, which include tau protein that has been hyperphosphorylated, are two characteristic that are crucial to the pathogenesis of AD.

2.1. Amyloid Beta Plaques

The amyloid precursor protein (APP), a bigger progenitor molecule that is extensively synthesized by neurons in the brain, blood cells, vasculature and astrocytes, is broken down into a 4 kDa fragment known as Aβ [3]. The β-secretase at the ectodomain and γ-secretase at intramembranous sites cleaved APP to produce the Aβ residue, while enzymes further break down Aβ monomers and oligomers. It is worth to mention that Aβ is toxic to neurons where free radicals are produced with Zn^{2+}, Fe^{3+}, and Cu^{2+}. The amount of soluble Aβ and the degree of neurological impairment in AD are highly correlated. Aβ accumulates due to defective clearance from abnormal cleavage of APP, therefore amyloid fibrils are the result of the polymerization of Aβ monomers into bigger insoluble fragments like Aβ 42 after they first form soluble oligomers (M.D, n.d.). Ultimately, neocortical neuritic plaques were found to be mostly composed of dense Aβ aggregates, which are pathologic characteristic of AD, in addition to NFTs of tau [3].

2.2. Tau Protein

Neurofibrillary tangles are abnormal accumulations of tau protein inside neurons. In healthy neurons, microtubules are internal support structures that help to route chemicals and nutrients from the cell body to the dendrites and axons. In healthy neurons, tau usually binds to microtubules and stabilizes them. However aberrant chemical changes associated with AD cause tau to detach from microtubules and attach themselves to other tau molecules, forming threads that eventually unite to form tangles inside neurons. These tangles interfere with the neuron's transport system, impairing synaptic transmission between neurons [4].

Recent research suggests that abnormal tau and Aβ proteins, among other factors, may combine intricately to generate brain changes linked to AD, as illustrated in the image. It seems that specific brain regions linked to memory accumulate abnormal tau. Aβ plaques arise interspersed with neurons. When Aβ levels become close to a tipping point, tau begins to spread quickly throughout the brain (Figure 1) [4].

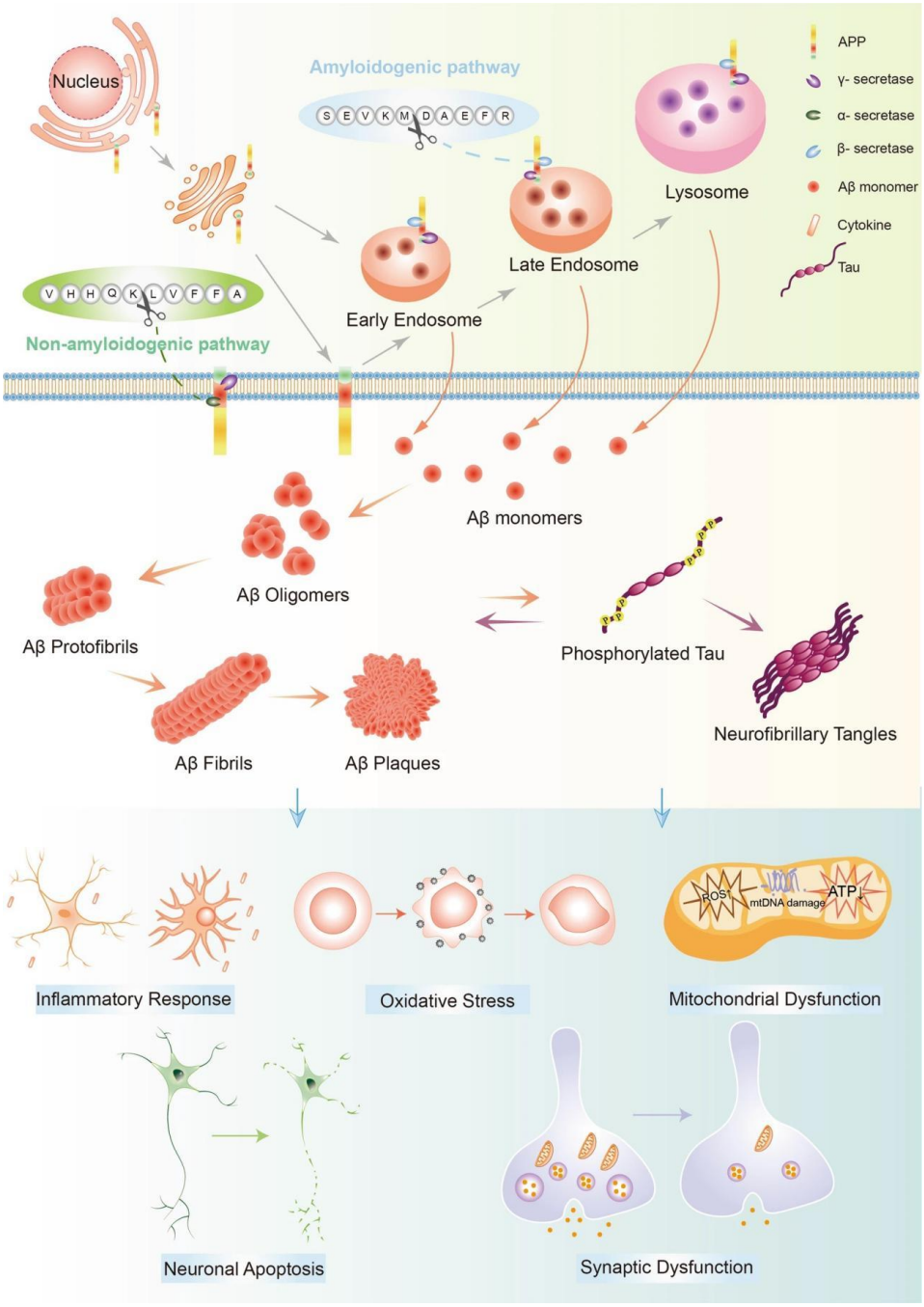

Figure 1. The mechanism of APPs and tau proteins, which lead to AD [5].

3. Lecanemab (Leqembi®) and Aducanumab (Aduhelm®) are Targets at Amyloid-beta Protofibrils

In the USA, lecanemab and aducanumab are two anti-amyloid mAbs that are authorized for the treatment of AD. The licensure of mAbs and their incorporation into clinical treatment are redefiding the field of AD therapy [2].

3.1. Lecanemab

Lecanemab is a humanised murine antibody mAb158 that is particularly designed to target soluble Aβ protofibrils, while it is also effective against insoluble fibrils as protofibrils are soluble aggregates of Aβ, which are neurotoxic and disrupted the electrical networks that contribute in memory function. Lecanemab has been demonstrated to preferentially minimise Aβ protofibrils, reduce pathogenic Aβ, and prevent deposition in the brain and cerebrospinal fluid of animal models of AD (Figure 2).

The unique target of acrylamide protofibril sets lecanemab apart from other anti-amyloid monoclonal antibodies. Lecanemab is the most efficient second-generation monoclonal antibody for immunodepleting Aβ protofibrils, particularly soluble protofibrils and oligomers. Lecanemab binds small protofibrils 100 times more strongly than aducanumab and large protofibrils 25 times more strongly than aducanumab, despite having a lower affinity for monomers. Several clinical trials have assessed lecanemab in people [6].

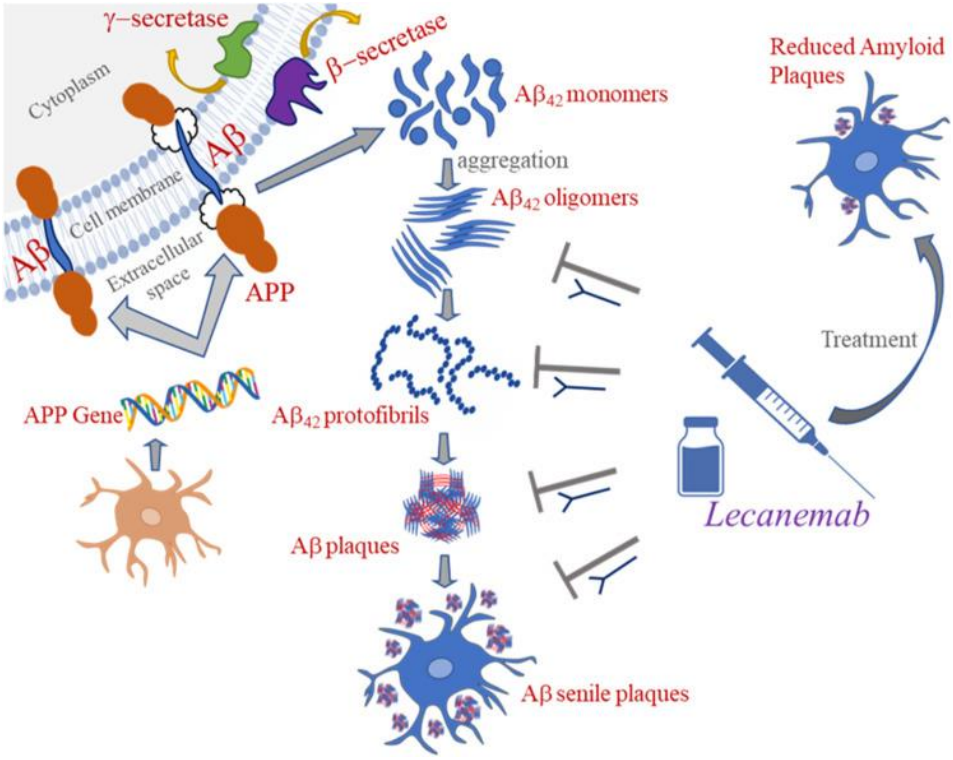

Figure 2. Lecanemab's biological action targets Aβ protofibrils [6].

As compared to a placebo, lacanemab caused an apparently less severe deterioration in cognition and function after 18 months, but it was also associated with side events and lowered amyloid indicators in early AD. Longer trials are required to determine lecanemab's safety and efficacy in the early stages of AD [7].

Lecanemab is prescribed by the FDA at a dose of 10mg/kg body weight. This dose needs to be diluted and provided as an intravenous infusion over the course of approximately one hour, once every two weeks. Lecanemab currently lacks any recognized contraindictions. However, it should be used cautiously in patients who have amyloid-related imaging abnormalities (ARIA). When modifying dosage recommendations for individuals with ARIA-Edema and ARIA-Hemorrhage, clinical symptoms, type, and radiographic severity should all be taken into account. [6].

3.2. Aducanumab

Aβ can occur in multiple forms within the neuritic plaques that neuropathologically characterize AD, including monomers, oligomers, fibrils, and protofibrils. Both protofibrils and oligomers can cause neurotoxicity. Consequently, it is believed that eliminating them using mAb therapy will aid in the management of AD.

Lecanemab and aducanumab have minimal affinity for the amyloid-beta monomer. When compared to fibrils, lecanemab bound to amyloid protofibrils ten times more strongly. Preferred binding sites for aducanumab are Aβ fibrils over protofibrils. These variations in mAb binding, according to Soderberg et al., may have implications for both the effectiveness of treatment and side effects.

A completely human IgG1 mAb with excellent affinity, aducanumab is designed to target a conformational epitope present on insoluble fibrils and aggregated soluble oligomers of Aβ, one of

the proteinopathies that cause AD. Aβ amino acids create a linear epitope that aducanumab binds to, as revealed by biochemical and structural investigations. As aducanumab binds to the N-terminus of Aβ, it takes on a longer form than other antibodies that have been studied previously. Because of its strong monovalent affinity, quick binding kinetics, and substantial avidity for aggregates rich in epitopes, aducanumab has proven to be an effective tool for distinguishing between Aβ monomers and oligomeric or fibrillar aggregates.

The brain stress of Aβ plaques is decreased by aducanumab's selectivity for aggregated Aβ forms. A lower amount of hyperphosphorylated tau was also observed in the cerebrospinal fluid (CSF) and in medial temporal neurofibrillary tangles in a limited subset of patients who had tau PET scans [8].

3.3. Gosuranemab

Gosuranemab is a mAb still under phase 2 investigation targeting tau protein. Gosuranemab is a humanised immunoglobulin G4 mAb that binds highly selectively to tau monomers and fibrils, specifically targeting N-terminal tau. In preclinical studies, gosuranemab successfully removed N-terminal tau from brain interstitial fluid, which reduced tau aggregation in cells. As a result, gosuranemab has been suggested as a potential treatment for tauopathies, possibly by preventing the absorption and neural transmission of the pathogenic tau that results in neurodegeneration. However, further investigation and clinical trials are still needed for gosuranemab [9].

4. Discussion

Although substantial clinical research of anti-amyloid immunotherapies has not produced a discernible clinical benefit for several decades, the advent of lecanemab and aducanumab encouraged the outcomes, along with earlier findings in mice models and preliminary human research, suggested that the focusing on amyloid-beta may be a viable strategy for improving AD. The result provided persuasive evidence that amyloid clearance by mAbs may be an advantageous treatment for AD, even in cases when symptoms are present.

It is imperative to tackle the therapeutic obstacles associated with AD as there are limitations of both lecanemab and aducanumab. Although targeting amyloid-beta has demonstrated potential, its constraints emphasize the intricacy of cognitive deterioration in later life. To optimize therapy success, the disease's heterogeneity calls for individualized methods and even combination medications. Furthermore, safety issues including the incidence of ARIA highlight the significance of all-encompassing approaches to control side effects.

In the brain, amyloid plaques accumulate gradually. Anti-amyloid medications bind to the protein in various ways and at different stages. Why this makes some medications better than others at treating AD is still a mystery to us. Comparing lecanemab directly to aducanumab, it has been found that the former binds to the most dangerous kind of amyloid protein with greater vigour. Furthermore, lecanemab also tends to eliminate amyloid considerably faster than aducanumab, as well as it shown a lower incidence rate of ARIA than aducanumab in clinical trials [10].

5. Conclusion

In conclusion, AD impacts millions of people globally, especially those at the age of 65. Therefore, mAbs that target tau protein or amyloid-beta plaques offer AD patients an efficient course of treatment, as well as improve the symptoms and quality of their life. According to current studies, lecanemab and aducanumab are two mAbs which target amyloid-beta protofibrils and fibrils, while gosuranemab is still experiencing phase 2 which is aimed at targeting tau protein, as two important mechanisms of AD that have been proposed are tau protein and amyloid-beta plaques. Studies have shown that both lecanemab and aducanumab have efficacy in reducing amyloid-beta plaques, while less ARIA presents adverse effects when administrating lecanemab compared to aducanumab. Both lecanemab and aducanumab provide effective treatment for AD, which slows the growth of AD and

reduces cognitive decline, however, safety issues should also be considered when administrated to AD patients. Moreover, more research should focus on long-term effects of the usage of mAbs on AD, as well as mAbs targeting the tau protein. It is also worth mentioning that the high cost of mAbs may limit the access of mAbs to all AD patients. Therefore, more effort should be paid on these gaps in order to reduce the incidence of AD as well as improve AD patient's life quality.

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