Dean&Francis
ISSN 2959-409X

Aducanumab and Lecanemab: Target Specificity, Mechanisms and Clinical Outcomes in Alzheimer's Disease

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Abstract:

Alzheimer's disease (AD) is one of the major unmet medical needs as a neurodegenerative disease associated with cognitive impairment and amyloid-beta (Aβ) accumulation. Unfortunately, current drug development for AD is based on treatment with only symptomatic therapies; there is no available drug able to influence the disease process. Anti-Aβ monoclonal antibodies have been shown as the promising strategy for AD therapy. However, little is known about the dissimilarities of these drugs in terms of target, mechanisms, and clinical effects. This review discusses the differences between two anti-Aβ antibodies – aducanumab and lecanemab, including target selectivity, mechanisms of action, structure, and clinical effectiveness. In particular, this review demonstrates that aducanumab interacts with the insoluble form of the protein, causing serious side effects, whereas lecanemab selectively binds the dangerous soluble protofibrillar form of Aβ. The importance of the state of Aβ aggregation for AD treatment has been revealed through the analysis of the drugs.

Keywords: Monoclonal antibody; Aducanumab; Lecanemab; amyloid-beta accumulation; Alzheimer's disease.

1. Introduction

The term Alzheimer's disease (AD) is associated with a progressively deteriorating neurodegenerative process leading to irreversible dementia, mainly targeting people aged over 65. It is one of the main causes of dementia worldwide and an increasing problem with the ageing population, putting tremendous strain on health care systems [1]. Clinically, AD is characterized by deterioration in memory and cognitive function and behavioral changes. However, there are no effective treatments developed to date that could stop or delay the course of disease. Thus, novel therapeutic approaches to tackle AD pathology are critically needed [2].

The exact cellular causes of AD remain unclear, but it is highly associated with the accumulation of extracellular insoluble amyloid-β (Aβ) plaques and microtubule tau protein in neurofibrillary tangles. The formation of Aβ plaques is related to amyloid precursor protein (APP), a transmembrane protein that is abundantly expressed in the brain, playing roles in iron

ISSN 2959-409X

transport, neural plasticity and synapse development. APP undergoes a series of abnormal enzymatic cleavages due to unknown pathological stimuli, catalyzed by a complex family of enzymes like β-secretase and γ -secretase proteases, resulting in Aβ peptide (Aβ 40 & Aβ 42) [3]. Aβ peptides are soluble monomers that group into amyloid fibrils, protofibrils, and oligomers, forming Aβ plaques in spaces between neurons (Figure 1). The progressive accumulation of Aβ fibrils ultimately results in the formation of Aβ plaques. It can disrupt synaptic functions, and trigger inflammatory responses in the brain [4].

Pharmacological treatment for AD includes acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and NMDA antagonist (memantine), which provide symptomatic treatment, but do not affect disease progression. Thus, therapies addressing the mechanism of AD (such as amyloid beta accumulation) are in high demand at present. Monoclonal antibodies (mAbs) represent an interesting and rapidly-developing class of anti-amyloid drugs aimed at selective binding of toxic peptide species. They may help remove toxic proteins from the brain and alleviate AD-associated neurodegeneration [2, 5].

Some of the most intensively-studied mAbs against Aβ are aducanumab and lecanemab. These antibodies differ in specificity and properties, which allows one to compare them [6]. First of all, lecanemab has higher affinity to soluble Aβ protofibrils, whereas aducanumab mainly binds Aβ fibrils and plaques. Moreover, lecanemab shows more stable results regarding clinical efficacy (it positively impacts cognitive functions) when compared to aducanumab. This makes both mAbs highly interesting objects for analysis [5, 7].

Therefore, this paper aims to compare the two antibodies, aducanumab and lecanemab, in terms of their ability to bind with specific receptors (amyloid species) in the brain, focusing our attention on drug-receptor interaction and their structural and functional specifics. Specificity and binding strength were considered, as well as the structure of two antibodies in relation to the structure of Aβ molecules.

2. Aβ Peptide Structure and Pathological Aggregation

The pathogenic importance of Aβ is critically determined by the conformational plasticity of Aβ and its ability to exist in various forms of aggregation. Even though Aβ peptides are endogenously produced in the brain, their aberrant folding and decreased clearance ability might promote the formation of aggregates in an inappropriate manner, resulting in the generation of pathological proteins [3, 4]. Aβ42 is one of several isoforms of Aβ, known to form β-sheet-rich structures due to the hydrophobicity of its C-terminal portion. In turn, these properties of the peptide promote intermolecular interactions, facilitating further stabilization of aggregates [4]. Aβ aggregation is considered to be a complex process that involves the gradual transition from a soluble monomer to a fibril aggregate. As shown in Figure 1, Aβ monomers can misfold to create dimers, oligomers, protofibrils, and ultimately fibrils leading to plaques with or without a dense core. As the aggregates increase in size, their solubility decreases [6]. The aggregation of such molecules leads to their accumulation in extracellular plaques. Moreover, numerous studies have proven that oligomers and protofibrils are likely to exert more toxic effects on neurons than mature plaques. In particular, the former types of aggregations can disrupt calcium metabolism, impairing synaptic activity and neuronal survival before the deposition of extensive plaques [8]. Also, protofibrils might activate inflammation by interacting with microglia and astrocytes, thereby accelerating neurodegeneration. Aβ aggregation exhibits structural diversity, which might impact the effectiveness of therapy with mAbs. Specifically, certain antibodies might target only insoluble fibril aggregations of Aβ, while others can selectively bind to soluble protofibrils. Therefore, the mode of action and therapeutic effect might differ significantly according to the type of aggregation recognized by antibodies [6].

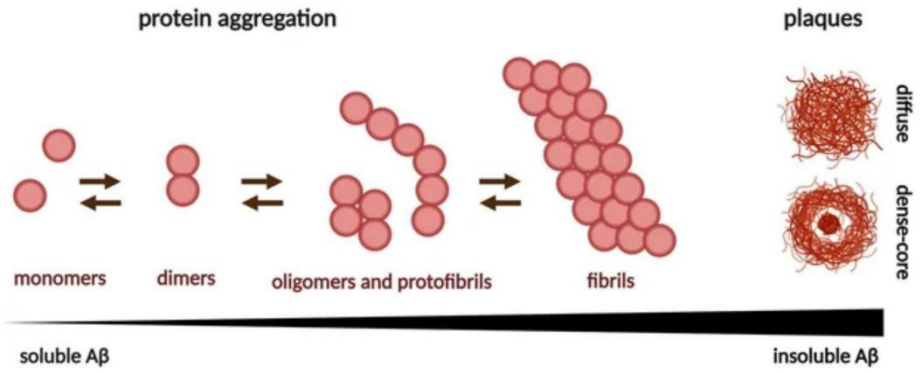

Fig. 1 Aggregation of Aβ. Adapted from source [6].

3. Structural Features of Aducanumab and Lecanemab

Both drugs, aducanumab and lecanemab, belong to the group of human mAbs IgG1, but have different conformational specificity and epitope recognition [7]. The difference is crucial since Aβ peptides undergo transformation from oligomers to protofibrils, mature fibrils, and finally, insoluble plaques during the progression of Alzheimer's disease. Each of the mentioned conformations has specific epitopes and different properties regarding the drug's affinity and efficiency [7, 9].

Aducanumab binds highly aggregated Aβ fibrils and prefers binding to Aβ peptides in a form of plaques and fibrils due to the increase in accessibility of binding sites while Aβ peptide aggregate becomes insoluble and turns into plaques. The binding site is activated by microglial cells via Fc receptors, which leads to clearance of Aβ peptides. On the other hand, high selectivity towards fibrils means that inflammation around blood vessels due to interaction of antibodies with vascular amyloid deposits can be an undesirable effect. Thus, Amyloid-related imaging abnormalities (ARIA) can occur due to high affinity to Aβ deposits [10]. Lecanemab demonstrates higher selectivity toward Aβ protofibrils rather than fibrillar peptides, which means that it cannot interact with vascular amyloid deposits. Protofibrils are known to be the most neurotoxic and toxic form of Aβ peptide aggregates, which implies the possible use of lecanemab as a potential therapeutic agent [8].

4. Molecular Mechanism of Drug–Receptor Interaction

The basis of molecular mechanisms that lie behind the effectiveness of Aβ-specific mAbs acting as potential medicines in treating AD is related to two key issues – the specificity of the interaction between the antigen and antibody as well as associated cell-receptor-mediated signal transduction. These are the two main features that determine not only the efficiency but also the toxicity of these medications. In terms of molecular mechanisms, these phenomena involve the formation of various types of non-covalent interactions including hydrogen bonding, hydrophobic interactions, electrostatic interactions, as well as shape complementarity and fitting between antibodies and their respective epitopes, which leads to certain specific binding between the latter [9].

Thus, aducanumab shows high selectivity of molecular mechanisms in connection with its specificity for recognizing N-terminal epitopes of aggregated forms of Aβ, with the preference for fibrillary structure characterized by numerous β-sheets. The specificity of this antibody is related to increased availability of epitopes in insoluble Aβ assemblies that can be effectively targeted by aducanumab and other therapeutic antibodies (Figure 2 A, B). A key feature of aducanumab mechanism involves the role of its Fc domain, namely, when bound to Aβ fibrils, aducanumab targets Fcγ receptors in the membranes of microglia. This process triggers activation of signaling pathways leading to restructuring of actin cytoskeleton and formation of lysosomal compartments in the microglial cell membrane, which enables effective uptake and degradation of Aβ fibril-antibody complexes [11]. At the same time, such a high avidity of aducanumab towards vascular Aβ fibrils results in FcγR-mediated activation of perivascular microglia and macrophages. As a result, this binding stimulates secretion of pro-inflammatory mediators, like tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), as well as increases vascular permeability, causing ARIA [10, 11].

On the contrary, the molecular basis of lecanemab involves a completely different pathway. Specifically, due to the structural complementarity, this antibody recognizes only soluble Aβ protofibrils, which means that the latter

ISSN 2959-409X

are its preferred targets (Figure 2 C, D). Unlike aducanumab, this therapeutic drug has low affinity towards fibrillar Aβ forms, which reduces interaction with vascular Aβ structures and prevents FcγR stimulation on perivascular microglia and macrophages [12]. Although IgG1-Fc domain of lecanemab can recognize Fcγ receptors, this process results in attenuated pro-inflammatory effects due to weak cross-linking caused by lower valence of soluble protofibrils compared to mature Aβ fibrils. Molecular mechanisms of action of lecanemab include the disruption of intermolecular Aβ interaction via steric hindrance caused by binding with soluble Aβ forms, preventing further fibrillization and neurotoxicity. In addition, the binding of lecanemab with Aβ protofibrils initiates FcγR-mediated uptake of the protofibril-antibody complex and reduces the toxic load of soluble Aβ [12].

These molecular specifics allow for distinguishing these two drugs from one another and provide grounds for explaining the reasons for differences in their efficiencies. Aducanumab provides efficient fibril-specific clearance of insoluble Aβ via FcγR activation; however, such mechanism is characterized by excessive inflammatory response. In turn, lecanemab employs an alternative mechanism based on selective recognition of protofibrils and associated neutralization of toxic oligomers as well as decreased inflammation mediated by FcγR.

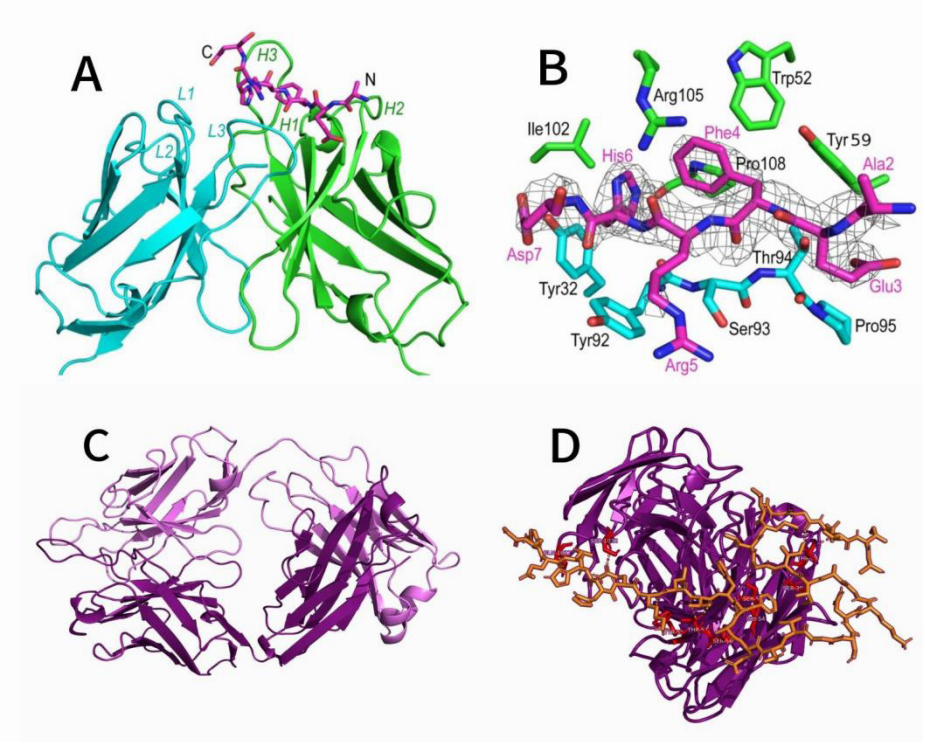

Fig. 2 Structures of Aducanumab and Lecanemab Bound to Aβ.

(A) Cartoon illustration of the AduFab–Aβ1-11 complex. Heavy and light chains are shown in green and cyan, respectively, while the Aβ1–11 peptide is shown in magenta.
(B) Detailed view of the binding interface highlighting key interacting residues and electron density surrounding the Aβ peptide.
(C) AlphaFold2-predicted structure of the lecanemab Fab, where heavy chain is in deep purple and light chain is in lavender.
(D) Predicted lecanemab Fab region (in purple) bound to Aβ (shown as orange sticks). Polar interfacing residues are labeled in red. Adapted from sources [11, 13].

5. Clinical Applications

In clinical practice, the phase 3 EMERGE and ENGAGE trials of aducanumab produced conflicting results, despite similar biomarker effects. High dose of aducanumab produced significant decrease in amyloid PET SUVR by 71% in EMERGE and 59% in ENGAGE trials by week 78, and reduced the levels of plasma p-tau181 in both groups, confirming significant target engagement. High dose aducanumab produced statistically significant 22% difference in CDR-SB slope from placebo group (−0.39; P = 0.012), and additional benefits on MMSE, ADAS-Cog13, and ADCS-ADL-MCI in EMERGE trial. On the contrary, in the ENGAGE trial, there were no significant improvements (CDR-SB difference 0.03; P = 0.833). The most

common side effect was ARIA-E in 35%–36% of patients who received high doses of aducanumab, especially those who had the ApoE ε4 allele. Aducanumab gained approval via an accelerated path for early Alzheimer's disease; however, due to safety issues, its use is restricted to patients monitored using MRI [14, 15].

In contrast to aducanumab, lecanemab shows a greater consistency in its effectiveness compared to aducanumab due to the more definite association of amyloid lowering with cognition. In particular, unlike aducanumab that had mixed results in the phase 3 EMERGE and ENGAGE trials (only 22% difference in CDR-SB in favor of aducanumab, P = 0.012 in EMERGE, whereas no significant clinical benefit observed in ENGAGE), lecanemab shows stable and reproducible cognitive and functional effects without substantial inconsistency between them. It should be noted that both drugs reduce the burden of amyloid PET, although the association of changes on biomarkers with clinical improvement is much more predictable with lecanemab. Moreover, safety aspects also speak in favor of lecanemab. Specifically, the high-dose groups of patients receiving aducanumab experienced 35%–36% of ARIA-E cases along with the higher risk among ApoE ε4 carriers, whereas this side effect occurred less frequently and was less severe with lecanemab [16, 17].

Both aducanumab and lecanemab serve as examples of how the same therapeutic approach may result in different applications in treating early AD. While aducanumab shows good biomarker effects, it is hampered by an inability to demonstrate clinically relevant effects and high levels of safety issues, requiring extensive imaging surveillance. In this way, lecanemab provides for more consistent biomarker-clinical correlation and lower safety impact, allowing for a more realistic implementation of the treatment. At the same time, the difference in the effects of both drugs allows for an important lesson to be learned about AD therapy in general: Soluble forms of neurotoxic β-amyloid molecules yield more predictable outcomes than mature plaques.

6. Conclusion

This study systematically compares aducanumab and lecanemab, two IgG1 monoclonal antibodies targeting amyloid-beta (Aβ) in early Alzheimer's disease. The literature reveals that there is a significant difference between the two antibodies in terms of their conformational specificity, mechanism of action, and clinical effectiveness. Aducanumab preferentially binds to Aβ fibrils and deposits while promoting the clearing of those by activating the Fcγ receptors on microglia, but causing considerable perivascular inflammation and high risk for ARIA-E, whereas lecanemab selectively binds to the soluble and toxic form of Aβ (protofibril), inhibiting its aggregation, eliciting mild inflammatory response, and providing better results.

As far as their clinical efficacy is concerned, there are clinical data suggesting that lecanemab performs better in biomarker-correlated cognitive improvements than aducanumab, whose Phase 3 trials yield inconsistent results in spite of considerable reduction of amyloid burden. These results strongly emphasize the importance of specific states of aggregation of Aβ in AD immunotherapy and provide direct answers to the problem discussed in the introduction.

The limitations of this review are the inclusion of only two antibodies without considering any long-term effects or combination treatment data. It is important in future research to engineer antibodies that have improved selectivity towards the protofibrils of β-amyloid protein. Research into combination treatments that focus on Aβ and tau, and long-term studies to demonstrate sustained efficacy and safety, would provide additional evidence to support the use of anti-Aβ immunotherapy in the clinic.

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