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Current status of the use of monoclonal antibodies for Alzheimer's disease

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Abstract:

Currently, there is no therapy proven to be ultimate in treating Alzheimer's disease (AD) that the World Health Organization (WHO) has named the condition its main global public health goal. Established treatments, such as cholinesterase inhibitors and memantine, primarily alleviate a number of manifestations of the problem, but they do not target the main problem at hand. Monoclonal antibodies like aducanumab and lecanemab are new drug classes with original mechanisms that rest on the Aβ hypothesis. Aducanumab is the first recombinant G1 human antibody, which can be given through intravenous drip and targets the amyloid plaques and, though its efficacy is still doubtful. Lecanemab, another of the FDA-undeclared antibodies yet displayed as potential early-phase trials that can neutralize soluble Aβ protofibrils. This essay weighs the AD treatment success, the safety profiles, and the potential side effects of aducanumab and lecanemab; it does so by comparing and contrasting these two therapies in terms of treating patients at different stages of the disease. Thus, through the application of the mAbs in this study, the essay becomes able to provide clues for the most effective use of these drugs. Such will eventually lead to the improved effectiveness of AD research and treatment.

Keywords: Aducanumab, Lecanemab, Alzheimer's disease.

1. Introduction

Currently, there is no therapy that has been proven that can fully recover Alzheimer's disease (AD), and the AD is defined as a "global public health priority" by the WHO. Cholinesterase inhibitors and memantine, a N-methyl-D-aspartate (NMDA) receptor antagonist, have historically been the most widely used pharmacologic therapy for patients with AD. However, the issue with this treatment is that this therapy cannot manage to cure AD [1]. All kinds of antibody therapeutics developed since 1992 have shown failures in phase three trials. The aducanumab is a recombinant human IgG1 antibody produced by Neurimmune from a library of peripheral blood lymphocytes from cognitively normal elderly patients, which was sold to Biogen in 2007 and has been under investigation [2]. The aducanumab is actually the first and only FDA approved drug used to remove the plaques which disrupt the major disease-causing processes that are critical to the progression of AD.

Next is the description of the current research significance of the application of monoclonal antibodies drugs for AD. As a new kind of approach to treating AD based on the Amyloid-beta (A-β) hypothesis, monoclonal antibodies have proved to be of great benefit considering the high efficiency for removing plaques, relatively minor side effects and target specificity. The significance of discussing the current research is that giving a better choice from Lecanemab (BAN2401) and Aducanumab is used for improving symptoms of AD through a comprehensive comparison and analysis.

The comparison is possible to reduce the risk of wasting budget on inappropriate aspects of research and help patients to get the most suitable treatment according to various stages of progression of the disease. Also, the analysis may be beneficial to reduce the possibility of AD with severe symptoms by using the most effective drugs at the early stage. Although the Lecanemab is not approved by the FDA to be used as a drug, the research can still be based on the research data and current trials. The content of the essay includes the introduction of the mechanism of AD which the monoclonal antibodies treatment is based on—the A-β hypothesis. In addition, the mechanism and current application of the monoclonal antibodies, which are specifically aducanumab and Lecanemab. On top of that, there will be a detailed introduction to the methods, results, safety and side effects of aducanumab and the Le-

canemab. Then a conclusion after the comparison is given to guide the therapy use of monoclonal antibodies for AD.

2. The A-β Hypothesis as a Mechanism of AD

It is important to note that there is no clear and certain mechanism or cause for AD. It was described as the formation of Amyloid plaque that causes the symptoms of AD. This essay only focuses on the A-β hypothesis which was one of the most accepted hypotheses.

There are mainly four parts that contribute to AD. First is about the Amyloid Precursor Protein (APP) being cleaved. In common situations, APP is defined as a normal protein that was derived from human brain. However, APP is able to be cleaved by different kinds of enzymes, leading to the production of various fragments. When it comes to causing AD, APP was cleaved by mainly two types of enzymes, which are beta-secretase and gamma-secretase enzyme. Amyloid beta peptides of varying length, particularly Aβ40 and Aβ42 were produced during this process. In addition, the Aβ42 is more likely to aggregate. And the above reaction is highly linked to the early-onset familial AD (EOFAD) [3].

The next section involves the Aggregation and plaque formation due to the properties of the Aβ42 peptide. The Aβ42 has the characteristic that is particularly sticky and tend to aggregate into oligomers and fabrils. This causes the result of formation of insoluble Amyloid plaque. Then is about the neuraltoxicity of the Amyloid plaques. The plaques are believed to affect and disrupt cell-to-cell communication and activate immune responses at the same time. When amyloid plaques aggregated together, it is possible to induce a cascade of pathological events, such as inflammation, oxidative stress, and synaptic dysfunction and eventually cause neuronal death [4].

The last section is the down stream effects caused by the accumulation of the amyloid beta. It is believed to trigger a series of downstream pathological events, including the formation of neurofibrillary tangles composed of hyperphosphorylated tau protein, which further contributes to dysfunction and loss.

3. Mechanism of Action of Monoclonal Antibody (mAb)

Monoclonal antibodies mainly play a role in treating diseases in three ways. The first mechanism of action includes direct combination with the role of the target. Monoclone first binds directly to pathogens or their toxins. Pathogens or toxins are substances that cause symptoms of human diseases. Combined reactions help neutralize their harmful effects. Moreover, monoclonal antibodies may attach specifically to viral proteins to inhibit viral particles' binding and entry into the cells.

MAb therapy can also regulate the immune system by way of suppression. In this article, we will show the two major mechanisms of mAb-induced cytotoxicity: the first is antibody-dependent cytotoxicity (ADCC), where monoclonal antibodies hold antigens of target cells; and next is complement-dependent cytotoxicity (CDC), where these antibodies are able to activate the complement system. Monoclonal antibodies attach themselves to antigens situated on the surface of cancer cells. After that, the Fc part of the mAb will be bound to the Fc receptors of other immune cells, such as NK cells, leading to the lysis of the target cell. Moreover, CDC (complement-dependent cytotoxicity) can be induced. In such a case, monoclonal antibodies can mobilize the complement system and assist in promoting the immune system's clash against pathogens (like viruses or bacteria) and even diseased cells.

Complemented proteins interact with the membrane-anchored mAb complex, which forms a membrane attack complex to lysis tissues of the target cell. In addition, the monoclonal antibodies can disrupt cell signaling by enabling the process of apoptosis. Such cross-reaction or blocking of cell surface receptors, or interfering with the cellular survival system, might result in cell death that is programmed.

Last but not least, monoclonal antibodies can inhibit cellular growth by preventing growth factor receptors or their ligands from migrating to the site of cell proliferation. Although this mechanism is not totally exclusive from other medical conditions, it is particularly effective in the treatment of AD where such growth factors were found to be disturbed.

4. Application Status of Monoclonal Drugs

4.1 Lecanemab

4.1.1 Mechanism

Using Lecanemab to treat cancer involves targeting Aβ plaques, activating the immune system, and reducing the burden on plaques.

In the first stage, Lecanemab selectively binds to soluble beta primary fiber, which is considered to be a key factor in plaque formation and AD-related toxicity. The accumulation of amyloid plaque is believed to cause symptoms of neurodegeneration. The second stage begins after lecanemab combines with these Aβ primary fibers. Lecanemab marks them and allows the body's immune system to clear them. Lecanemab facilitates microglial cells to be activated to attack and remove the amyloid-β-Aβ complex. The last phase of the drug, lecanemab, results in reducing amyloid plaques in the brain, likely leading to a slower speed

of progression of the disease. To achieve this, lecanemab is expected to target and decrease the level of plaques for to reduce their neurotoxic impacts, generate improvements in the cognitive function of patients, and ensure that the decline happens at a slow pace.

4.1.2 Results

Recent clinical trials, specifically the Phase 3 CLARITY AD study, have shown that lecanemab can delay the progression of cognitive fail and alleviate age-related neurodecline in patients with early cases of AD. A number of subjects, with diverse profiles of mild cognitive impairment or mild Alzheimer's dementia, participated in the study. There were significant improvements in cognitive function as shown by some of the well-accepted tools that test the functioning of the brain, which include the ADAS-Cog score and the CDR-SB. Lecanemab reduced the number of plaques in the brain in imaging studies of the treatment cohorts. All these data collectively mean that the capability of lecanemab in zeroing down on early Cutaneous AD stages.

4.1.3 Safety assessment

It must be mentioned that although lecanemab is effective in slowing down the rate of neurodegenerative changes, it still shows some side effects. It is composed of imaging abnormalities that are amyloid-related (ARIA). This symptom may be followed by the occurrence of the most severe side effect, which is brain swelling and even brain bleed, which might be detected directly from an MRI examination.

Apart from ARIA-related amyloid-assocated imaging abnormalities, the main side effect of lecanemab is infusion-related reactions. These side effects include a set of the symptoms (fever, chills, nausea, headache, rash, hypotension) [5].

4.2 Aducanumab

4.2.1 Mechanism

Regarding the progression of the disease theory, the mechanism associated with the treatment of AD using aducanumab is similar to that of lecanemab, and it is based on three main stages. In the preliminary stage, aducanumab is specifically directed toward the aggregation of amyloid beta, including soluble oligomers and insoluble fibrils. Consequently, the second stage involves aducanumab being the binding platform and hence, amyloid beta plaques attributed to be the immune system-groomed so as to flag them for immunity [6]. The next step is the activation of the brain microglia, the resident immunocompetent cells, in order to clear away the aggregated amyloid-beta fragments. Consequently, this mechanism is aimed at reducing the amyloid plaque in the brain tissue and, therefore, it has a potential to ameliorate the natural course of AD. By working up these plaques, namely, by disarming their neurotoxicity, aducanumab expects to curb their effect on cognitive function.

4.2.2 Results

The outcomes obtained from clinical trials utilizing aducanumab, a drug for Alzheimer's, are however somewhat ambiguous. For example, the recent Phase 3 EMERGE research reported small to medium positive effects, where aducanumab appeared to have the potential to slow down the progression of cognitive decline in patients with early-stage AD. The participants who were included in the research were diagnosed as either mild cognitive impairment or mild form of Alzheimer's dementia. The results were that aducanumab treatment in early-stage AD prevented or, in some cases, sustained improvements in cognitive functioning. This evidence was based on the patient's memory span-related tests like the Mini-Mental State Examination (MMSE) and assessments conducted in memory clinics. Moreover, brain imaging identified a decrease in amyloid plaques in the participants treated with aducanumab, which in turn supported its potential efficacy as a remedy for early-stage AD [7].

4.2.3 Security assessment

Nonetheless, the most encountered effects, are amyloid-related imaging abnormalities (ARIA), with main two forms, including brain swelling (ARIA-E) and microhemorrhage (ARIA-H). While the most commonly reported side effects consist of headache, dizziness, fever, and chills, there is still a possibility of the so-called infusion-related reactions [8].

The contending factor that has drawn skepticism or criticism in the approval of aducanumab is the fact that trials have given mixed results, but it raises the concerns of clinical risk versus benefit. Even though in-progress studies, up to the approval phase, are pivotal, however, long-term programs and post-marketing safety surveillance are imperative to give conclusive evidence and insights into the therapy's safety and correct protocol.

5. Recommended monoclonal antibodies for the treatment of different disease courses

Both lecanemab and aducanumab are monoclonal antibodies created to manage Alzheimer's ailment by countering amyloid-beta plaques in the human brain. Comparing and contrasting their application in different stages of AD, as well as considering their mechanisms, clinical results, and safety data can be employed [9].

Originally, researchers generally specified lecanemab for early AD due to their robust effectiveness in the early

stage clinical trial, and the mechanism of action that focuses on combating amyloid-beta protofibrils and enhancing cognitive function. In fact, including aducanumab can also be contemplated, particularly in patients with significant evidence of amyloid plaque burden. Nevertheless, the conflicting results indicate the importance of a thoughtful process of decision-making and a careful monitoring of these patients [10].

In moderate to severe cases of AD, the evidence supporting the use of lecanemab and aducanumab in such cases is mainly derived from first-stages of intervention. Although studies to evaluate these drugs in moderate to severe AD have been conducted, their indications are not well-established. Furthermore, additional studies are required to establish proper treatment recommendations.

Though both lecanemab and aducanumab have demonstrated the potential to treat early AD by targeting amyloid-beta plaques, lecanemab has shown at this stage a more consistent efficacy indicator in the current clinical trials. Adverse findings regarding aducanumab make it necessary to observe careful patient inclusion and monitoring of patients. Besides, for the treatment of the advanced stage of Alzheimer's, further research should be carried out to determine the effectiveness of the medications in this stage [11,12].

6. Conclusion

The comparison between lecanemab and aducanumab illustrates the changing prospects in the treatment of Alzheimer's disease (AD), highlighting the ability of monoclonal antibodies (mAbs) to influence disease progression through the selective targeting of amyloid beta (Aβ). Being effective in patients with early disease stages, lecanemab is a reliable choice because of its action on the early Aβ plaques, and though it may slightly affect plaque burden, chances for side effects are quite low. Lecanemab, still waiting for FDA approval, is showing promise in AD pharmacotherapy field based on the preliminary clinical data available.

Aducanumab, FDA approved mAb for AD, targets aggregated Aβ forms, particularly oligomers and fibrils. Intertwined with conflicting clinical data and aspirations to obtain approval, aducanumab remains a feasible plan, mainly for those individuals with noticeable amyloid plaques. On the other hand, care must be taken in the selection and monitoring of the patients during its use due to the high probability of developing ARIA (amyloid-related imaging abnormalities) and some other side effects.

Nonetheless, drug treatment with each of the mAbs noted stops at moderate-to-severe stages of AD, such as lecanemab and aducanumab. More research is needed on the treatment of later stages of the disease by lecanemab and aducanumab. Only the evidence of an early onset of AD has been documented, which stresses the need for adherence to more studies to maximize the benefits of AD treatment therapies.

To sum it up, even though both lecanemab and aducanumab have shown that they can treat patients with early AD by targeting amyloid plaques, lecanemab appears to have better and more stable efficacy in the treatment. It also shows that the understanding of the stage of the disease and the patient's unique traits are of paramount importance, in order to venture this strategy with full effectiveness. The remaining investigations and the post-marketing surveillance will be instrumental in the preparation of further guidelines for the use of these mAbs and the determined goal of enhancing the quality of patients' life and refining our plans in the treatment of AD.

References

[1] H. W. Haddad et al. Aducanumab, a novel anti-amyloid monoclonal antibody, for the treatment of Alzheimer's disease: A comprehensive review. Health Psychology Research, 2022, 10(1).

[2] Takeda M. Development of monoclonal antibody therapeutics for Alzheimer's disease. Taiwanese Journal of Psychiatry, 2022, 36(4): 148.

[3] Chen G, Guo et al. Amyloid Beta: Structure, Biology and Structure-Based Therapeutic Development. Acta Pharmacologica Sinica, 2017, 38(9): 1205-1235.

[4] Villamor N, et al. Mechanism of Action and Resistance to Monoclonal Antibody Therapy. Seminars in Oncology, 2003, 30(4): 424-433.

[5] Vitek GE, et al. Lecanemab (BAN2401): An Anti–Beta-Amyloid Monoclonal Antibody for the Treatment of Alzheimer Disease. Expert Opinion on Investigational Drugs, 2023, 32(2).

[6] Salloway S, et al. Aducanumab and the Amyloid Hypothesis: The Alzheimer Disease Battle. JAMA Neurology, 2022, 79(1): 13-21.

[7] Swanson CJ, et al. A Randomized, Double-Blind, Phase 2b Proof-of-Concept Clinical Trial in Early Alzheimer's Disease with Aducanumab, an Anti-Aβ Protofibril Antibody. Alzheimers Research & Therapy, 2021, 13(1): 80.

[8] Hoy SM. Aducanumab: First Approval. Drugs, 2023, 83(4): 359-365.

[9] Alzheimer's Association. 2023 Alzheimer's Disease Facts and Figures. Alzheimer's & Dementia, 2023, 19(1): 1-91.

[10] Biogen. Aducanumab (Aduhelm). Biogen.com, 2021 [2024-07-06]. www.biogen.com/en_us/aduhelm.html.

[11] Cummings J, et al. Alzheimer's Disease Drug Development Pipeline: 2023. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2023, 9(1): e12470.

[12] Doody RS, et al. A Phase 3 Trial of Aducanumab for Alzheimer's Disease. New England Journal of Medicine, 2019, 381(9): 803-816.