Taking Donanemab as an Example: A Discussion on the Treatment of Alzheimer's Disease (AD) with Second-Generation Anti-Aβ Monoclonal Antibodies

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Abstract: Alzheimer's Disease (AD) is the most common form of dementia in older adults. The high incidence and high rate of disability put a heavy burden on patients' families and society. Abnormal deposition and aggregation of β-amyloid (Aβ) in the brain are the core pathological mechanisms of the onset and the progression of AD, which are also the important target of the current drug development. In the past few years, the second generation anti-Aβ monotoclonal antibodies, represented by, donanumab, have been successively approved for the market release, which is a new direction of the disease-modifying treatment for AD. However, there are still many shortcoming of the existing drugs in the aspect of the eligibility of patient, the longterm eficacy and safety. In this article, we systematically explain the targeted mechanism of action of Donanemab against Aβ, review the preclinical research and the key data of clinical trial of Donanemab in comprehensively, and analyze the limit and the controversy of the practical application of this class of drugs. This review can give a comprehensive reference for the rational clinical application of Donanemab and help to clarify the strength and weakness of the second generation anti-Aβ antibodies. Considering the complicated pathogenesis of AD, the single target intervention is still not enough to get the good therapeutic effect. The future research should focus on the strategy of combination therapy to improve the clinical safety and the longterm benefit of donanliumab.

Keywords: Alzheimer's Disease; B-Amyloid; Donanemab; Monoclonal Antibody; Mechanism of Action; Clinical Trial

1. Introduction

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder, and it is the most common form of dementia, characterized primarily by memory loss, cognitive decline and behavioral disturbances. The patients of AD usually need the continuous and intensive care, which is not only a job that need a lot of time, but also a financial burden of the families. The prevalence among the adults aged 65 and older is about 6.6% in China, and it doubles every five years; the prevalence among the adults aged 80 and older is as high as 22%. Therefore, AD is not only a disease, but has been a social issue. It is a big challenge to the increasingly aging society in China [1].

To date, the treatment of AD is still closely related to the medication. The traditional therapy is to delay the process of the disease. The main category is cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists. These drugs play a certain role in delaying the process of neurological decline, however, they cannot reverse or stop the process of neurological deterioration, and the effect of these drugs will decrease as the disease progress. The second generation of the of the A beta (beta-amyloid, A B) monoclonal antibody (m A b) drug represented by Donanemab has improved the clinical efficacy, safety and specificity of the first generation of the A B m A b s such as aducanumab. It has made great progress in improving the cognitive function of the patients with the early- to mid-stage A D, slowing down the process of the disease in the patients with AD, and keeping the long-term stability in the patients, so it is a hope for the treatment of A D.

In view of the above-mentioned advances in the current research, in this article, we review the molecular mechanisms, the preclinical studies, the clinical trials, the limitations and the future prospects of the second generation of A B mAbs, represented by donanumab, The goal is to understand the current status of this class of drugs and to give some scientific reason and

guidance for the AD drug development.

2. Pathogenic Mechanisms of AD

The pathogenic mechanisms of AD are complicated. After it is identified in 1906, many theories about its pathogenesis have been raised out. Now, the most influential theoretical framework is the amyloid cascade hypothesis, which is composed of mainly two parts: the abnormal aggregation of the A beta, and the abnormal phosphorylation of tau protein.

APP (amyloid precursor protein) is a large protein which is embedded in the neuronal plasma membrane. When APP is cleaved by the enzyme called as the beta-secretase, it produces a fragment called as C99. When the C99 is cleaved by the secretase called as the gamma-secretase, a fragment A B42 is formed. Since the terminal residues of A B42 are strong hydrophobic, it aggregates in the aqueous environment of the brain to form more stable structures. The initial aggregation of A B42 requires a high energy barrier. But once the nucleation occurs the aggregation of A B42 is easier. In this way it forms amyloid plaques and tangles.

In the healthy young brains, A is cleared in large quantities before it can aggregate much; as the people get older, the body may clear A of A if 42 is not good, and that is why the AD incidence is positively correlated with the age.

Early-onset AD (EOAD) is also associated to genetic studies. So far, there are three genes known for being associated to EOAD: the APP, the presenilin 1 (PSEN1) and the PSEN2. These genes lead to abnormal APP processing by different mechanisms, and in all the cases change the production or the processing of the A beta [2]. A beta damages the neurons by different mechanisms. Among them, the oligomers, that are form by pre-amyloid aggregation, are strongly neurotoxic. Soluble toxic oligomers, and in particular the type 1 oligomers, that are also called synaptotoxins, disrupt the normal synaptic signaling and so the cognitive function. A beta affects mitochondrial function, so that the synaptic transmission is disrupted and we have neurodegeneration. A beta oligomers and plaques trigger inflammatory responses in the brain and they have different effects on microglial reactivity [3].

Tau protein is an important protein in the healthy neuron, which is the one which is to stabilize microtubules so as to ensure the transport of the nutrients and other functions. Abnormal A B deposition out side of the neurons bring abnormalities in the intracellular signaling pathways, that leads to the hyperphosphorylation of tau. When, the tau protein is in the form of hyperphosphorylation, it loses its ability to stabilize the microtubules, it leads to the structural instability of the microtubules and in the end, prevents the neurons to do any normal physiological functions. Also, the hyperphosphorylated tau protein misfolds and aggregates and in the end, it forms the insoluble tangle in the neuron, which is known as the neurofibrillary tangles.

The aforementioned Aβ pathology and tau pathology together consist of the amyloid cascade hypothesis, which is still the central theory for explaining the pathogenesis of AD. Although this hypothesis has some limitations, for example, from the studies, the data from genetic, imaging, clinical and biochemical point of view show that maybe the etiology of AD is more complicated [4]. However, it is the important theoretical foundation for the current AD drug development, and is the cake of theory for explaining the complex pathogenesis of the disease. The developing of the second generation of Aβ mAb drug is based precisely on this theory. The clinical benefit of such drugs is undoubtedly the strong scientific support for the validity and rationality of this theory.

3. Molecular Mechanism and Preclinical Studies of Donanemab

Donanemab is a humanized immunoglobulin G1 mAb that does not bind to Aβ oligomers but instead specifically targets mature, stable Aβ plaques in the brain, ultimately exerting a plaque-clearing effect. During the progression of AD, newly formed Aβ deposits undergo a series of post-translational modifications. Among these, the glutamic acid at the N-terminus of the Aβ peptide is cyclized by pyroglutamylase to form pyroglutamate (pGlu), resulting in N3pG-Aβ. Donanumab specifically recognizes Aβ modified by pyroglutamate at the third position of the N-terminus and, through its Fc segment, recruits and activates microglia in the brain to clear plaques with the aid of their phagocytic activity [5]. The N3pG-Aβ epitope targeted by donanliumab is found exclusively in mature amyloid plaques that have accumulated over time in the brain, rather than in soluble Aβ monomers circulating in the bloodstream. This

allows the antibody to avoid the peripheral antigen-sink effect and concentrate its action more effectively on lesions within the brain. The TRAILBLAZER-ALZ 4 study compared Donanemab with aducanumab, a first-generation Aβ mAb. Results showed that at 6, 12, and 18 months of treatment, the proportion of participants achieving plaque clearance in the Donanemab group was 37.9%, 70.0%, and 76.8%, respectively, while the aducanumab group achieved 1.6%, 24.6%, and 43.1%, respectively ($P < 0.001$). The median time to plaque clearance was 359 days and 568 days for the Donanemab and aducanumab groups, respectively ($P < 0.001$) [6]. This trial demonstrates that Donanemab is significantly superior to aducanumab in both the speed and extent of plaque clearance.

The preclinical proof of concept for donanumab can be traced back to the seminal study by DeMattos et al. The researchers designed an antibody (anti-Aβp3-x) targeting plaques deposited in the brains of AD patients and tested it in an aged PDAPP mouse model [7]. The results demonstrated that, following therapeutic plaque reduction studies in the mouse model using anti-Aβp3-42 antibodies, mE8 significantly reduced mature Aβ plaque deposits in the brains of the mice regardless of whether the antibody's functional effect was maximal (mE8-IgG2a) or minimal (mE8-IgG1), and that the clearance mechanism did not require the antibody to bind to soluble Aβ peptides [7]. This preclinical study demonstrated the potent clearance capacity of Donanemab, developed based on this mechanism, against pre-existing Aβ deposits, as well as the feasibility of this drug's targeting strategy.

Furthermore, another study used a combination of N3pG and the BACE inhibitor LY2811376 to treat AD transgenic mice, and the results showed that this regimen could clear more than 80% of Aβ deposits in the model mice; this result also provides strong evidence for the therapeutic efficacy of donanumab.

The mechanism of action and therapeutic effects of a drug are often closely linked to the processes by which it acts within the body; the ADME (absorption, distribution, metabolism, and excretion) properties of donanligumab are of central importance in determining its clinical efficacy and safety. Due to its nature as a large-molecule protein, its pharmacokinetic (PK) and pharmacodynamic (PD) characteristics differ fundamentally from those of traditional small-molecule drugs.

Regarding absorption, like all therapeutic mAbs, donanliumab cannot be effectively absorbed via the oral route and must be administered by intravenous infusion, reaching peak plasma concentrations several hours after intravenous injection [8]. Regarding distribution, as a macromolecule, donanligumab is primarily distributed within the vascular space and the extracellular space. Its steady-state volume of distribution (Vss) is typically close to or slightly greater than the plasma volume, indicating that it does not readily penetrate tissues extensively. Studies have shown that although the integrity of the blood-brain barrier (BBB) allows for extremely low permeability of IgG antibodies (typically <0.1% of plasma concentration enters the cerebrospinal fluid), in patients with AD, the integrity of the BBB may be compromised due to Aβ pathology itself and associated neuroinflammation [9], allowing donanligumab to enter the brain parenchyma at low but pharmacologically active concentrations. With regard to metabolism and excretion, donanligumab is not metabolized by the hepatic cytochrome P450 enzyme system but is primarily degraded through proteolytic pathways in tissues throughout the body. Its clearance occurs primarily through two pathways: first, a non-specific pathway, in which proteolytic enzymes in various tissues throughout the body degrade it into amino acids and small peptides, which are subsequently reused in the body's normal amino acid pool; and second, a specific pathway, namely target-mediated drug disposition (TMDD). At the onset of treatment, the abundance of N3pG-modified Aβ targets in the brain is high; donanumab can rapidly and specifically bind to them, forming immune complexes that are subsequently phagocytosed and degraded by microglia. This is the core mechanism underlying its plaque clearance.

4. Clinical Trials of Donanliumab and Related Challenges

4.1 Clinical Progress

TRAILBLAZER-ALZ 2, conducted by Eli Lilly, is a multicenter, randomized, double-blind, placebo-controlled, 18-month Phase III clinical trial of donanliumab. A total of 1,736 patients with early-stage AD who had PET-confirmed

cerebral amyloid deposits and tau protein abnormalities were enrolled in the trial; ultimately, 1,320 patients completed the study. Participants were randomized in a 1:1 ratio to receive either donanliumab (n=860) or placebo (n=876) via intravenous infusion every 4 weeks for 72 weeks [5]. Once patients in the donateglib group meet the criteria for discontinuation, they will be switched to placebo treatment in a blinded manner. The trial results indicate that, compared with subjects receiving placebo, patients receiving antibody treatment experienced a statistically significant delay in disease progression. Among all patients who completed the trial, the between-group difference in the least squares mean (LSM) of the iADS score was 2.92 in the donanliumab group compared with the placebo group ($P < 0.001$), and the between-group difference in CDR-SB score change was −0.70 ($P < 0.001$); both results were statistically significant [5]. The trial also included a 78-week double-blind long-term extension study (LTE), which showed that at 3 years, the Donanemab early treatment group exhibited a slower decline of −1.2 points on the CDR-SB compared to the external control cohort (ADNI) (95% CI −1.7, −0.7); Patients who completed the 52-week treatment course continued to demonstrate sustained clinical benefit at 3 years, requiring only a limited course of treatment [10]. Key Phase III clinical trial results for Donanemab demonstrate that the drug effectively clears amyloid plaques in the brain and significantly delays cognitive decline and disease progression in AD, showing clear disease-modifying benefits and supporting its value as a disease-modifying treatment for AD.

4.2 Real-World Application Examples of Donanliumab

Donanliumab is also used in the real world clinical practice now. In a recent published study, the authors did systematic testing and evaluation in a 78-year-old female AD patient with donanliumab. After six treatments with donanliumab, the A B burden decreased to 7.02C, which is the criteria for the discontinuation, and the tau protein deposits were visually decreased to mild degree compared with the baseline. This case shows the short treatment duration and the quick onset of action of Donanemab, and also strongly confirms the effective clearance of A B by Donanemab. More importantly, it shows that the one big advantage of Donanemab over the previous AD medicines is the limited treatment duration. That is, once the patients meet the criteria of the discontinuation after a period of treatment, they don not need to take the medicine. It is a big step in the history of AD drugs and plays a key role on the alleviating the financial burden on the patients families [11].

4.3 Risks and Challenges Associated with Donanliumab

In the TRAILBLAZER-ALZ 2 trial, 24.0% of participants in the donanliumab group exhibited amyloid-related imaging abnormalities such as edema or effusion, which was 21.9% higher than in the placebo group [5]. Additionally, the incidence of infusion-related reactions was 8.2% higher in the donanliumab group than in the placebo group. Studies have also noted that donanliumab, like other Aβ mAbs, carries a black box warning regarding the risk of amyloid imaging abnormalities, which manifest as potentially fatal brain swelling [12]. To date, the long-term efficacy and safety of donanliumab remain undetermined.

Aβ mAbs, including donanumab, are currently indicated only for the treatment of early-stage AD and are restricted to patients with confirmed Aβ pathology via positron emission tomography (PET) or cerebrospinal fluid (CSF) testing [13]. Similar to other AD treatments, given that our current understanding of the pathogenesis of AD is not yet fully clear and Aβ is not the sole pathogenic factor mediating the onset and progression of AD, this also limits the therapeutic efficacy of Aβ antibody drugs to some extent [14].

5. Conclusion

As a novel immunotherapeutic agent that directly targets Aβ, donanligumab is able to clear A B deposits in the brain by immune-mediated mechanism. It has shown significant clinical efficacy in the treatment of early stage AD, which provides a new direction for the intervention of AD. It has been confirmed in clinical that donanligumab can slow the disease progression. The limited treatment time can also reduce the burden on patients and their families and society. It should be noted that the short- and long-term safety of donanligumab needs to be monitored and evaluated and currently only can be applied in

the patients with early stage AD. Since the pathogenesis of AD is complicated, in future the treatment strategy might shift to combined treatment in the pathways of tau protein, neuroinflammation and metabolic disorders. With the development in this field, donanligumab will bring more benefits for the clinical treatment of AD.

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