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Antibody Drugs in Alzheimer's Disease

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Abstract. Alzheimer's disease is one of the important causes of Alzheimer's disease. The prevalence rate has been increasing in recent years, which is a hot issue for the medical community. In view of the pathogenesis of Alzheimer's disease is still not exactly diagnosed, the research and development of related drugs is not particularly ideal. Existing drugs mostly stay in symptomatic treatment. However, in recent years, the medical community has gradually turned to causative treatment. Among them, disease-modifying therapy (DMT) is the most frequently studied drug at present, accounting for 82.5% of the total drugs under consideration. Among the DMT-class drugs, 16 (equivalent to 15.4%) are specifically designed as anti-amyloid beta (Aβ) monoclonal antibodies (Mabs), while 11 (accounting for 10.6%) target tau proteins with monoclonal antibody technology. Through reviewing past literature and comparing data, this paper takes Aducanumab, Lecanemab, and CCTM2 as examples to explore the therapeutic principles and make a summary.

Keywords: Alzheimer's disease; immunotherapy; Aducanumab; Lecanemab; CCTM2.

1. Introduction

Dementia, particularly Alzheimer's disease, represents the most prevalent form of cognitive decline affecting individuals aged 65 and above globally [1]. This neurodegenerative condition systematically impairs memory and cognitive functions, eventually hindering even fundamental task execution. Underlying this progressive disorder damages brain neurons, which are vital for human activities such as thought processes, verbal communication, and locomotion. The course of AD is a long-term process, related changes in the brain begin to appear 20 years or more before clinical symptoms develop [2]. In patients having Alzheimer' s, neurons in the parts of the brain responsible for memory, language, and thinking are damaged first, leading to the initial symptoms related to memory, language, and thinking. When such symptoms are serious enough to interfere with a person's ability to perform a task, it is called Alzheimer's disease.

Alzheimer's disease has a relatively long course, from the brain changes that affect the affected person to impaired memory and thinking function with each episode and eventually physical disability, a series of processes known as the Alzheimer's continuum. Alzheimer's disease has a relatively long course, from the brain changes that affect the affected person to impaired memory and thinking function with each episode and eventually physical disability, a series of processes known as the Alzheimer's continuum. The continuum of Alzheimer's disease consists of three broad stages: preclinical Alzheimer's disease, mild cognitive impairment (MCI) due to Alzheimer's disease, and dementia due to Alzheimer's disease, commonly referred to as Alzheimer's-type dementia. Furthermore, Alzheimer's-type dementia is further classified into mild, moderate, and severe dementia .

Over the years, researchers have identified various changes in the brain that hinder the transmission of chemical signals, which affect thinking, learning, and daily functioning caused by Alzheimer's disease. Among all the changes, there are two major changes in the brain. One is the clumps of protein fragments, known as β-amyloid plaques, that accumulate outside nerve cells and the accumulation of proteins inside the nerve cells, the other is atrophy (reduced brain volume) caused by neurodegeneration and other factors [3].

Beta-amyloid and tau proteins have different roles in Alzheimer's disease. The accumulation of plaques and small beta-amyloids can potentially damage neurons by disrupting communication between nerve cells at the synapse. Inside nerve cells, aggregates of tau protein hinder the transport of nutrients and other molecules, disrupting essential functions and survival, and impairing the connections between nerve cells. Additionally, the aggregation of beta-amyloid and tau proteins triggers detrimental effects on neuronal and other brain cells, a condition known as neurodegeneration, which is a fundamental characteristic of Alzheimer's disease. These toxic proteins are hypothesized to stimulate microglial activity, the brain's resident immune cells, responsible for clearing out waste and debris from damaged or compromised cells. Persistent inflammation ensues when the microglial capacity to manage these duties is compromised [4]. Furthermore, apart from the accumulation of Beta-amyloid and tau proteins, atrophy (reduced brain volume) caused by neurodegeneration is another main change in the brain associated with Alzheimer's disease. While some level of brain shrinkage is common in older adults, it accelerates even in cognitively healthy people with Alzheimer's disease [5].

According to recent findings, the accumulation of beta-amyloid protein exhibits a notable increase approximately two decades prior to symptom onset, typically aligning with the age of onset for individuals carrying inherited genetic predispositions to the condition [6]. In another study, it was also found that abnormal levels of neurofilament light chain protein (a biomarker for neurodegenerative diseases) began 22 years before expected symptoms appeared [7]. The third research group discovers that levels of various types of tau increase two years before the characteristic mature tau aggregates appear in Alzheimer's disease, as beta-amyloid aggregates into amyloid plaques [8]. Furthermore, the researchers also find that that glucose metabolism begins to decline 18 years before the expected symptoms, and that brain atrophy starts 13 years before the expected symptoms [9].

The aforementioned neurological transformations serve as definitive biomarkers for Alzheimer's disease. These biomarkers consist of quantifiable biological alterations that signal the presence and potential risk associated with the condition. In the stage of preclinical Alzheimer’s disease, even in individuals who do not yet show memory loss or thinking, there are still significant measurable changes, including abnormal increases in the levels and distribution of beta-amyloid and tau proteins, as well as reduced glucose metabolism shown on PET scans, and changes in tau proteins in the cerebrospinal fluid (CSF), which are important biomarkers to diagnose the Alzheimer’ s disease and important breakthrough in the treatment of the disease [10].

According to the survey, there are about 50 million people suffering from dementia worldwide, of which about two out of three are Alzheimer's disease patients. With the increasing degree of population aging, the number of people with dementia is predicted to increase to 152 million by 2050. The number of people with Alzheimer's disease will also surge [11].

Despite the large global population affected by Alzheimer's and other forms of dementia, with over 55 million individuals, there remains an absence of a verified prevention method and a cure for this condition [12]. Owing to the uncertainty of the pathogenesis of Alzheimer’s disease, the development of its drugs is particularly difficult. There have been more than 50 drug candidates successfully passing Phase II clinical trials, but all have failed in Phase III trials over the past 20 years. The FDA has only approved five drugs to treat AD in the last 20 years, including Tacrine, Donepezil, Rivastigmine, Galantamine, and Memantine, all of which are small molecule drugs, with the first four being Acetylcholinase (AchE) inhibitors and Memantine is N-Methyl-D-aspartic acid (NMDA) receptor antagonist. However, all of the 5 drugs are symptomatic treatments, mainly targeted to improve cognitive and memory disorders rather than preventing or delaying the progression of the disease. Furthermore, both the AchE and NMDA receptor antagonists have serious side effects. Therefore, they are not suitable for long-term treatment[13].

At present, most of the drug research and development is based on various hypotheses and theories of Alzheimer’s disease. With the "beta-amyloid hypothesis" and "Tau hypothesis" these two theories

are gradually accepted. New drug development gradually shifts to the targeted therapy for beta-amyloid plaques and tau toxic proteins. At present, the widely recognized drugs for the treatment of beta-amyloid protein are Aducanumab, Lecanemab, and Donanemab. Similarly, there are major breakthroughs in targeting toxic tau proteins, the most representative of which is TTCM2. All the targeted drugs discussed above are monoclonal antibody drugs.

The purpose of this study is to investigate the current status of existing agents for the treatment of AD dementia, including β-amyloid-targeting and tau-toxic protein targeting. Taking Aducanumab, Lecanemab, and TTCM-2 as examples, the advantages and disadvantages are analyzed comprehensively with the help of previous literature.

2. Aducanumab

Developed by Biogen, Aducanumab is a high-quality recombinant human immunoglobulin (IgG1) monoclonal antibody derived from a meticulously selected pool of blood samples from elderly individuals displaying no symptoms of cognitive decline or steady regression, showing its ability to selectively eliminate amyloid beta aggregates [14]. Aducanumab is mainly applied in treating MCI and mild dementia caused by Alzheimer's disease. In June 2021, Aducanumab became the first Alzheimer's disease (AD) pathophysiological basis drug approved by the U.S. Food and Drug Administration (FDA) under the accelerated approval pathway.

In Alzheimer's Disease (AD), the conversion of soluble neurotoxic oligomers from monomeric Amyloid Beta (Aβ) molecules precedes the accumulation of insoluble polymer aggregates, typically manifesting as amyloid plaques [15]. The amyloid hypothesis posits that the development of these misfolded protein deposits instigates enhanced toxic effects, culminating in the formation of Tau neurofibrillary tangles, disrupted vasculature, inflammation, and ultimately, neuronal demise and dementia [16]. Monomer Aβ dimerizes, which is the reason for the formation of aggregates. In fact, the presence of Aβ dimers in patients with Alzheimer's disease correlates with the clinical symptoms of the disease[17]. Thus, anti-amyloid therapy demonstrates a promising treatment strategy for Alzheimer's disease (AD) by preventing the pathological oligomerization of Aβ and protecting the brain from amyloidosis. At present, immunotherapy is the most advanced method of anti-amyloid therapy, and it is defined as active immunity when the immune system is stimulated to produce its antibodies, and passive immunity when exogenous antibodies are used. [18]. Compared with passive immunity, Passive immunization promotes high antibody titers, and interruption of treatment can resolve adverse events, especially for the elderly who may not have active immunotherapy and induce adverse reactions [19,20]. Moreover, researchers find that, in addition to inhibiting toxic Aβ oligomerization or inducing microglia to clear plaques, monoclonal antibodies also have anti-inflammatory effects, reducing the production of pro-inflammatory cytokines and associated neuroinflammation [21,22].

Aducanumab is kind of a new generation of monoclonal anti-Aβ antibodies that specifically target Aβ aggregates. However, better than previous anti-Aβ, Aducanumab shows higher selectivity to the Aβ aggregates (including soluble oligomers and insoluble fibril) and combines them together [23,24]. When the binding happens, it activates the microglia and attracts them to the site of the Aβ aggregates. Once the microglia reach the site of Aβ plaque, it isolates the core and prevents the formation of further oligomers. In addition to the isolation, accomplishing the phagocytosis of the deposits and cleaning the toxic substance from the brain before the toxic substance damages neurons. the binding of the Aβ oligomer to the metabolic receptor is prevented by the binding between the microglia and the Aβ oligomer, thus avoiding membrane depolarization and neuronal calcium overload. Last but not least, due to the Aducanumab's own capability to bind to the fibrils, it is able to competitively bind with fibrils, reducing secondary nucleation of Aβ aggregation [14]. Furthermore, Aducanumab distinguishes monomers from oligomers or fibrous aggregates based on weak univalent affinity, fast binding kinetics, and strong affinity for epitope-rich aggregates [25]. This means Aducanumab may

more accurately target Aβ aggregates, reduce the accidental killing of normal β-amyloid protein, and better achieve precision medicine.

Even though Aducanumab looks promising in the treatment of Alzheimer's disease, its safety concerns still need to be taken into account. According to a 2012 Phase 1B randomized trial called PRIME, which includes patients with MCI and mild AD disease, ARIA (Amyloid-related imaging abnormalities) is the most common side effect of use of the drug, and increases with increased dose and ApoE4 genotype (a genetic risk factor for AD). Moreover, The Food and Drug Administration's recent authorization of Aducanumab via the expedited approval process is predicated on the medication's demonstrated efficacy in clearing amyloid-beta plaques. However, there is no conclusive evidence that Aβ plaque removal is associated with a reduction in cognitive or functional decline. Additionally, the two Phase III trials after accelerated approval, EMERGE, and ENGAGE, show different results, even after posthoc analysis, the data obtained were not sufficient to support the efficacy of ADU. Finally, there is plenty of debate about the cost-effectiveness and safety of ADUs. Currently, Biogen is working on the design of the confirmatory study "ENVISION" required by the FDA, which is expected to be completed in 2026 [23].

3. Lecanemab

Lecanemab, commercially known as Leqembi, has recently achieved full approval status from the U.S. Food and Drug Administration (FDA) for the treatment of early-stage Alzheimer's disease, encompassing mild cognitive impairment (MCI) and mild dementia associated with Alzheimer's. This innovative therapy targets beta-amyloid plaques, which are pivotal biomarkers in Alzheimer's pathophysiology, by effectively reducing their presence in the brain [26].

Lecanemab is a recombinant humanized immunoglobulin γ1 (IgG1) anti-amyloid monoclonal antibody that binds to amyloid oligomers, fibrils, and insoluble fibrils. Fibril represents the high molecular weight species of soluble amyloid protein and preferentially binds to Lecanemab [27]. As demonstrated in preclinical trials, mAb158, or the mouse version of Lecanemab, preferentially binds to amyloid beta protein (Aβ) fibrils over Aβ monomers, and also shows a preference for binding to aggregated amyloid fibrils compared to the fibrils themselves. mAb158 can identify soluble amyloid aggregates in human brain extracts from Alzheimer's patients. Since mAb158 is a homolog to Lecanemab, it indicates that Lecanemab has a beneficial effect on the elimination of amyloid beta [28]. In the Clarity AD clinical phase 3 trial, a comprehensive analysis revealed a more pronounced reduction in biomarkers indicative of amyloid, tau, neurodegeneration, and plasma GFAP in the Lecanemab group compared to the placebo group. Notably, the neuronal injury marker NfL demonstrated a lesser sensitivity to neurodegeneration dynamics, exhibiting a slower rate of change relative to the other markers [29]. Additionally, Lecanemab, in the treatment of early Alzheimer's Disease (AD), has consistently demonstrated a dose-dependent decrease in both clinical decline and amyloid burden within the brain. An 18-month, multicenter, double-blind, placebo-controlled clinical trial employing a Bayesian design revealed that administration of Lecanemab, relative to placebo, leads to a sustained and dose-dependent improvement in clinical outcomes. Concurrently, there was a dose-dependent reduction in amyloid PET scan findings throughout the treatment period, findings further reinforced by complementary cerebrospinal fluid (CSF) biomarker results. For the evaluation of Aβ clearance, clinical efficacy, and safety, intravenous dosing at 10 mg/kg every two weeks is recommended. This data pertains to a Phase 3 clinical trial [30].

Infusion reactions and ARIA are the main side effects of Lecanemab. An infusion reaction usually occurs during the first 2 treatments, mainly appearing during or within a few hours after the infusion. Generally, infusion reaction symptoms usually resolve within 24 hours, which means it can be solved at home [30]. In the clarity AD study, 26.4% of participants taking Lecanemab experienced an infusion reaction, usually mild to moderate in severity [30]. In the current meta-analysis, Lecanemab significantly increases the risk of ARIA-E and ARIA-H compared to the placebo group. In the clarity AD (Phase 3) trial, 12.6% of all MRI-based participants developed ARIA; 2.8% had symptoms. In

Phase 2 participants, 9.9% of those taking a dose of 10 mg/kg every two weeks developed radiological ARIA (i.e., the dose administered in the clarity AD Phase 3 trial) [29]. Furthermore, The APOE genotype should also be considered in the course of treatment. The APOE genotype is a risk factor for AD, and the APOE-ε4 allele is considered to be the strongest genetic modifier for late-onset Alzheimer's disease [30]. APOE-e 4 individuals, especially homozygous ones, had limited therapeutic effects with drug therapy and significantly increased ARIA [30]. In the clarity AD (Phase 3) trial, 12.6% of all MRI-based participants developed ARIA; 2.8% had symptoms [29]. Therefore, APOE genotyping of all therapeutic candidates prior to initiation of Lecanemab therapy is able to inform risk discussions and help guide safety considerations [31].

4. CCTM-2

Developed by a multi-institution team of neuroscientists led by the University of Texas Medical Division (UTMB), toxic tau conformation-specific monoclonal antibody-2(TTCM2) is a monoclonal antibody to disease-fighting tau proteins that selectively identify pathological tau aggregates in the brain tissue of patients with AD, Lewy body dementia (DLB), and progressive supranuclear palsy (PSP). At the same time, ttcm2 can also effectively inhibit tau seeding activity, which is an important mechanism of tau disease progression [32].

Since tau pathology correlates better with the severity of dementia than amyloid-beta lesions, suggesting that targeting tau may be more effective for improving cognitive function in Alzheimer's disease than removing amyloid-beta [33]. Most current clinical trials targeting tau are tau immunotherapies. However, this type of immunotherapy is still in its early stages [33].

Tau protein is mainly an intracellular protein, whether in normal physiological form or pathological form, in a variety of sizes of aggregates that are able to form neurofibrillary tangles [34]. Most of the pathological proteins are present in neurons, but a few individuals and some of the pathological proteins of tau disease are present in glial cells. However, interestingly, most of the tau antibodies currently in clinical trials have been described as acting only outside the cell because of their limited ability to penetrate cellular compartments, where tau accumulates. This appears to reduce their efficacy because of the inability to recruit phagocytosis to degrade tau antibody complexes and prevent toxic TAU protein seeding [34].

TTCM2 has a high degree of specificity and powerful penetration. Studies have shown that TTCM2 exhibits A high affinity only for neurotoxic tau oligomers, but not for tau monomers, Aβ, or α-synuclein in healthy cells. This property ensures the safety and efficacy of the treatment. Moreover, TTCM2 is more significantly active in the brains of older mice, further validating its potential in the treatment of Alzheimer's disease [32]. Additionally, compared with traditional intravenous injection, nasal spray administration has the advantages of simple operation, high patient acceptance, rapid drug action, and wide distribution. To enhance TTCM2's penetration, the research team added a lipid microcell to it, an innovative design that significantly improved the antibody's affinity to cell membranes, helping it to easily penetrate nasal mucosa and nerve cells. Experimental results showed that after receiving nasal spray TTCM2 treatment, TTCM2 was widely distributed in various brain regions within about 3 hours, including key parts of the hippocampus, cortex, and cerebellum. Even more exciting is that TTCM2 can enter the interior of neuron cells and bind tightly to tau protein aggregates, thus playing a targeted therapeutic role [32].

5. Conclusion

Through the research, this paper mainly explores the treatment principle of Alzheimer's disease and the existing medical situation, carrying out in-depth research on the immunotherapy of Alzheimer's disease. Existing immunotherapies are mainly divided into monoclonal antibodies targeting amyloid beta and monoclonal antibodies targeting tau. By studying and comparing the existing experimental data, this paper finds that compared with the traditional treatment for alleviating cognitive impairment, immunotherapy aims to have a more accurate targeted treatment for the cause of treatment,

fundamentally alleviating the damage of early Alzheimer's disease on cognitive function. However, it should be noted that the development of immunotherapy is still in the preliminary stage, and patients can still experience side effects such as ARIA after taking the drug. In addition, the development of tau drugs is still stuck in the animal model stage, it should be noted that there is no perfect animal model, and the choice of relevant research tools depends on the specific problem being studied. Given that the association between the beta starch model and the tangling accumulation of tau protein and cognitive decline in humans remains unestablished, it is possible that future optimization of brain extraction protocols to obtain broader Alzheimer's disease pathology and more in-depth characterization of underlying cognitive deficits should be one of the priorities of future immunotherapy modeling studies.

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