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Recent Advances on Early Diagnosis and Immunotherapy Drug for Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease that has seriously affected public health. Although the scientists have studied AD deeply and explored several therapeutic strategies, there is still no complete cure. Therefore, early diagnosis and treatment is the key to addressing AD problems. This review includes currently accepted pathological hypotheses for Alzheimer's disease (AD), such as β -amyloid (A β) deposition, tau phosphorylation, cholinergic hypothesis, and inflammatory response. The early diagnosis of AD, including neuropsychological assessment, biomarker detection, and imaging techniques, highlights a new immunotherapy drug called lecanemab and its clinical trial results. It can reduce Aβ levels, improve cognitive function, and delay the progression of the disease. But problems remain regarding side effects, costs, and patient compliance. At present, AD treatment is facing challenges, which needs to explore new therapeutic targets and drugs, and optimize therapeutic strategies. At the same time, strengthening the research and application of early diagnosis technology, improving the awareness of AD among patients and their families, is help to improve the quality of life of patients and reduce the social and family burden. Countries need to invest more to promote the development of AD research and clinical practice.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative old age disease that is complex, multifactorial, unalterable, and progres-sive in nature. According to the World Health Organization, the number of people living with dementia worldwide is increasing year by year, and is expected to climb to 152 million by 2050. However, acquired factors such as cerebrovascular disease, diabetes, hypertension, obesity and dyslipidemia increase the risk of AD development. The clinical manifestations of the disease mainly include memory impairment, cognitive impairment, and impaired language and visuospatial function, and the symptoms gradually worsen with the course of the disease. Often accompanied by impaired abstract thinking and computational power, personality and behavioral changes such as apathy, aggression, and depression occur. With these symptoms, the disease imposes a significant financial burden on patients and their caregivers, while having a profound

impact on their lives. There is no radical treatment and lacks widely available disease-modifying drug therapy, and current research focus is on understanding the pathological mechanisms of AD, such as β -amyloid, abnormal tau metabolism and inflammatory response, to develop new treatments. This review discusses the pathological mechanisms of AD, early diagnosis techniques, and conventional therapeutic agents, the latter mainly introducing the emerging drug lecanemab.

2. Current Understanding of AD Pathomechanism

2.1 β -Amyloid (A β) Deposition Theory

Different hypotheses have been proposed for AD in recent years, but currently, the amyloid hypothesis remains the most widely recognized and validated mechanism. Amyloidosis is a complex clinical and pathological phenomenon in which the formed amyloid protein accumulates in various organs and cells of the body, forming amyloid plaques that eventually gradually lead to organ dysfunction. Amyloid plaques are made up of amyloid proteins. Amyloid β peptide (A β) is the major component that plays an important role in the pathogenesis of AD and is considered to be the main cause of AD [1]. Amyloid precursor protein (APP) is a concentrated in neuronal synapses single transmembrane protein, highly expressed in the brain, produced by brain neurons, blood vessels, blood cells and a small amount of astrocytes, then APP is cut by two hydrolysate, namely extracellular β secretase and intracellular γ. They form the A β after their interaction, and this process is illustrated in Figure 1.

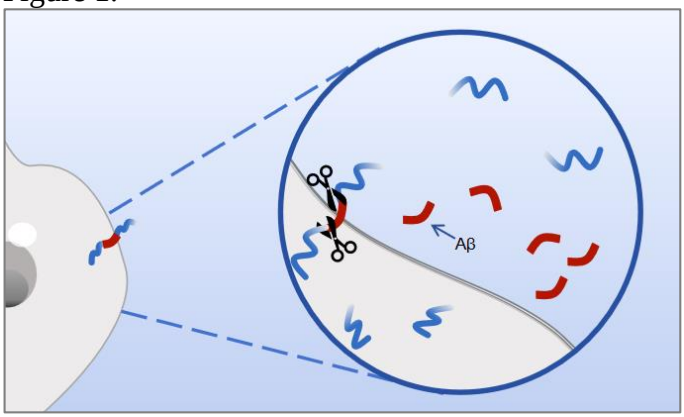

Figure 1: Aβ is released from APP by β-secretase and y-secretase

APP mutation can lead to increase A β synthesis. Monomeric A β fragments are soluble substances that cause metabolic problems when an imbalance between synthesis and clearance, which leads to protein misfolding, aggregation and extracellular accumulation, and ultimately the formation of amyloid plaque. As shown in Figure 2. At the same time, the high concentration of A β may induce APP synthesis and trigger amyloidosis in peripheral neurons [2]. Partial A β misfolds and accumulates in the brain to form hydrophobic extracellular oligomers presented in plaques and fibers, and β plaques initially develop in the basal, temporal, and orbitofrontal neocortical regions of the brain, later to the entire neocortex, hippocampus, amygdala, diencephalon, and basal ganglia. In critical cases, A β plaques can also be found in the midbrain, lower brainstem, and cerebellar cortex. As a consequence of this process, the neurons and synapses involved in memory processes, learning, and other cognitive functions are damaged, leading to the typical cognitive decline [3].

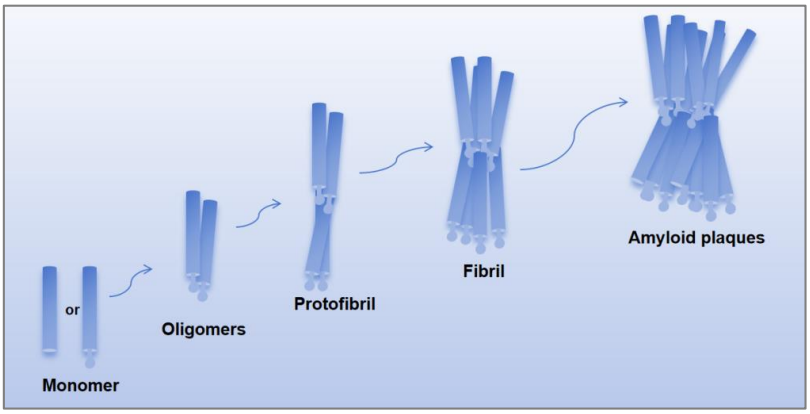

Figure 2: A β deposition process

2.2 The Hyperphosphorylation of the Tau Protein

Tau is a microtubule-associated protein, and the main physiological functions of this protein include microtubule stimulation, tubulin polymerization, microtubule stabilization, and transport of intracellular organelles. Abnormal filaments of hyperphosphorylated tau can at some stages tangle to form paired helical filaments (PHF) and accumulate in the perinuclear cytoplasm, axons and dendrites, leading to the loss of cytoskeletal microtubules and tubulin-related proteins. This protein loses its function in microtubule synthesis and stabilization, and becomes the main component of NFT (neurofibrillary tangle) in the brain of AD patients, which is shown in Figure 3.

It leads to neuronal damage and promoting cytotoxicity [4].

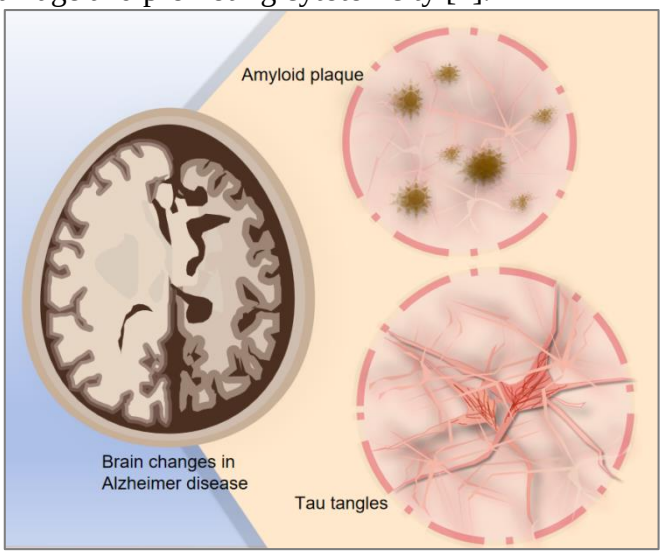

Figure 3: Brain changes in Alzheimer disease

2.3 The Cholinergic Hypothesis

In the 1970s, neocortical and presynaptic cholinergic defects were reported to be associated with choline acetyltransferase (ChAT), suggesting a cholinergic hypothesis in the AD. Acetylcholine is synthesized by the choline and acetyl-coenzyme A (acetyl coenzyme A) in the cytoplasm of cholinergic neurons and transported to synaptic vesicles via the vesicular acetylcholine transporter (VAChT). In the brain, acetylcholine is involved in memory, attention, sensory information, learning, and other key functions. Meanwhile, A β is thought to affect cholinergic

neurotransmission and lead to reduced choline uptake and acetylcholine release [5].

2.4 Neuroinflammation

In addition to the above two mechanisms, neuroinflammation is considered a key link in the pathogenesis of Alzheimer's disease (AD). Impaired vasculature causes the brain to lack adequate blood and nutrients, as well as remove debris from metabolites. By activating astrocytes and microglia, this condition triggers chronic inflammation, which then damages neurons and aggravates the pathological changes of AD [6]. Therefore, the research and development of drugs to inhibit neuroinflammation has become an important topic.

3. Current Diagnosis and Technology

3.1 Diagnosis

In addition to clinical symptoms and neuropsychological tests, the diagnosis of AD also includes biomarkers, imaging techniques, and genetics. Biomarkers such as β -amyloid (A β) deposition and neuroinflammatory response have potential for early diagnosis of AD, and further research on the correlation of these markers and disease can provide a strong basis for early diagnosis. Advances in neuroimaging technologies also provide possibilities for early diagnosis of AD, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning, which can visually observe structural and functional changes in the brain and become a diagnostic basis. However, it should be noted that there is a nonlinear association between Aβ content in CSF and PET scan [7]. Due to its relative invasiveness, CSF sampling may not be applicable for elderly patients. Non-invasive imaging methods such as fluorodeoxyglucose PET can provide insight into AD-related brain metabolism [8]. Neuroimaging techniques can detect these changes early and provide strong evidence for diagnosis, but a definitive diagnosis usually requires histological verification postmortem. Through multidisciplinary studies on biomarkers, neuroimaging and genetics, we can more accurately identify people at high risk of AD and provide timely intervention and treatment for patients. In the future, with the continuous development of science and technology, we are expected to make more breakthroughs in the early diagnosis of AD, and benefit patients and families.

3.2 Risk Factors

Studies have shown that about 70% of AD risk can be traced back to genetic factors. However, some acquired factors can also increase the risk of AD, such as cerebrovascular disease, diabetes mellitus, hypertension, obesity, and dyslipidemia, all of which may lead to an increased risk for the development of AD. Furthermore, from an individual perspective, reductions in cognitive level, social activity, and physical activity frequency were also identified as risk factors for AD. Psychosocial factors, such as depression, anxiety, stress, and chronic psychological distress, are also associated with an increased risk of AD [9]. Some risk factors are shown in Figure 4. However, healthy lifestyles and habits have an important role in slowing down the process of Alzheimer's disease (AD). This includes regular exercise, a Mediterranean diet, intellectual activity, and higher education. Multi-domain comprehensive interventions, such as lifestyle modifications, maintaining mental health, and controlling cardiovascular risk factors, can also help maintain or improve cognitive function and prevent Alzheimer's disease in the elderly. These measures are essential for the health and well-being of older age.

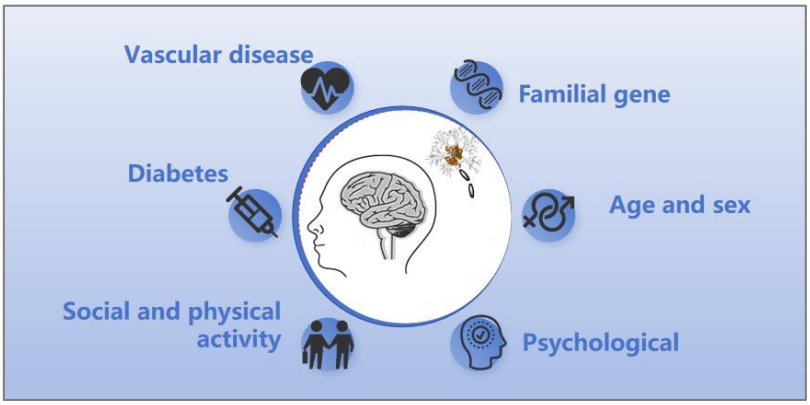

Figure 4: Some genetic and acquired risk factors as shown

4. Conventional Drug Therapy

AD medication mainly involves the symptomatic control of disease progression, including the control of cognitive, behavioral, and psychological symptoms. There are four types of commonly used drugs: donepezil, memantine, galantamine, and rivastizemine, which belong to anticholinesterase inhibitors and antiglutaminergic drugs. The former aims to increase acetylcholine levels in the brain, correct acetylcholine deficiency in AD patients, and promote neuronal information transfer and memory function. The latter regulates glutamate levels, achieved by a noncompetitive antagonist of the n-methyl-d-aspartate (NMDA) receptor. AD prevention also includes active immunization, which produces vaccines against A β 42, and passive immunization, which uses monoclonal antibodies (mAb) and immunoglobulin (Ig) [10]. The latter application is discussed in detail below.

4.1 Cholinesterase inhibitors and n-methyl-d-aspartate (NMDA) receptor antagonists

In the 1970s, premature loss of cholinergic neurons in the basal forebrain was observed in the brain of Alzheimer's disease patients, and the cholinergic hypothesis of senile memory dysfunction was proposed. Neurochemical evidence suggests reduced acetylcholine acetyltransferase in cognition-related areas in the brain of AD patients. Cholinergic neurotransmission plays a key role in impaired cognitive function in AD and adult dementia. Cholinesterase inhibitors (ChE-Is) are effective treatments for AD, which can improve cognitive function and delay the disease [11]. ChE-Is on the market include donepezil, livastin, and galantamine, while tacrine has been stopped due to hepatotoxicity.

The nmda receptors allow calcium access in neurotransmission but are hyperactive in AD, resulting in excess calcium ions, triggering excitotoxicity and cell death. Memantine acts as a non-competitive antagonist by binding to nmda receptors. Unfortunately, currently approved drugs only temporarily relieve the symptoms of this complex disease, so new treatments for AD are being sought and developed.

4.2 Passive immunotherapy against amyloid protein

Treatment of AD by amyloid removal has been proposed for over 20 years. Starting with the first effective A β immunotherapy, AN1792, removing A β from the brain has already proven feasible and arguable. However, some experimental deaths caused safety problems, which prompted research from active immunization to passive immunization, mainly through symptomatic treatment with monoclonal antibodies.

Current drugs developed include Bapineuzumab, Solanezumab, Gantenerumab, Aducanumab, Lecanemab, etc,which is shown in table 1. Bapineuzumab is a humanized monoclonal antibody (hmAb), preclinical studies have shown that it can combine the different forms of A β, reduce the amount of intracranial A β protein in mice, improve animal memory, and improve cognitive performance in patients with mild to moderate AD. Solanezumab is an anti-amyloid mAB that binds to a soluble A β peptide. Its phase 3 trial of patients with mild AD for 80 weeks showed improved cognitive and functional loss. However, two later phase 3 trials failed to show its effect in delaying cognitive decline and improving function and are therefore controversial. Gantenerumab Is an anti-amyloid immunoglobulin G1(IgG1) hmAb that removes aggregated A β plaques by phagocytosis. A phase 2 clinical study was terminated with no significant results and clearance of amyloid plaques in the brain was also lower than expected. Aducanumab Is a complete human IgG 1 mAb that targets A β, selectively binds aggregated A β fibrils and reduces A β plaques in the brains of AD patients.

Table 1: Immune antibody types and the mechanisms of action, of Passive immunotherapy drugs

Medication	Immune antibody types	Mechanism of action
Bapineuzumab	the humanized monoclonal antibodies	Binound A β monomers, oligomers and fibers
Solanezumab	antiamyloid monoclonal antibodies	Binding to the soluble A β peptide
Gantenerumab	immunoglobulin G1 hmAb	Removal of the aggregated A β plaques by phagocytosis
Aducanumab		Can selectively bind to the aggregated A β -protofibrils

4.3 The emerging drug—Lecanemab

The experience with the aforementioned drugs offers new hope for the development of other monoclonal antibodies—lecanemab. As a humanized monoclonal IgG 1 antibody, it highly targets soluble and insoluble A β, which can reduce A β plaques in the brain and prevent its shape. What distinguishes Lecanemab from other anti-amyloid monoclonal antibodies is its preference for A β fibril targets.

A β fibrils are large, soluble A β aggregates that exhibit neurotoxicity by impairing the electrophysiological mechanisms associated with memory function. Furthermore, moderately sized A β oligomers and protofibrils have proven to be the most neurotoxic species among them, suggesting that targeting protofibril A β may be an effective therapeutic strategy.

4.4 Clinical study of lecanemab

A double-blind, randomized, placebo-controlled study showed that 856 patients were randomized to five dose regimens or placebo. With open-label extension and blank periods, patients receive 10mg / kg lecanemab every two weeks,with a median duration of 24 months. At 12 and 18 months of core treatment, brain amyloid measurements showed decreased PET, plasma biomarker changes, and slowed cognitive decline in the experimental group. The clinical progression rate was similar in the blank period, and treatment differences remained after withdrawal. This suggests that Lecanemab treatment significantly reduces amyloid plaques and slows clinical decline [12]. Clarity AD Is an 18-month, multicenter, double-blind, phase-trial study. Patients diagnosed with early Alzheimer's disease using PET or cerebrospinal fluid received placebo or 10mg / kg IV. Results showed that Lecanemab was associated with relative preservation of health-related quality of

life(HRQoL)and caregiver burden, with consistent benefits within both different QoL scales and scale subdomains [13].

Another article stated a randomized, double-blind, phase 2b proof-of-concept clinical trial against early Alzheimer's disease. The trial uses a Bayesian design to assess the safety and efficacy of lecanemab at placebo and at different doses. At 18 months, 10 mg / kg lecanemab showing a difference in drug placebo of 27% and 30%, ADCOMS, ADAS-Cog 14 of 56% and 47%, CDR-SB of 33% and 26%, and CSF biomarker supportive treatment effect. In this study, an intravenous dose of 10mg / kg to CMAb every 2 weeks was considered the best dose to test A β clearance, clinical efficacy and safety in phase 3 clinical trials [14].

In a systematic review and meta-analysis of randomized clinical trials including data from all four reported randomized controlled trials comparing the efficacy of lecanemab and placebo in the treatment of cognitive decline in AD. The article proposed that lecanemab has statistically significant positive efficacy in cognition, function and behavior in patients with early AD, but the actual clinical significance has not been determined. And proposed that the true meaning of the observed change is questionable because it has never been correctly analyzed for the possibility of temporal changes and random effects. Meanwhile, each study variable was different in the key biomarkers, and therefore, could not be compared. These limitations deserve our further thinking and exploration [15].

5. Conclusions

Alzheimer's Disease (AD) is a chronic, progressive neurodegenerative disease characterized by the gradual decline of the brain's memory, thinking and behavior. With the deepening of medical research, researchers have gained a more comprehensive understanding of the pathological mechanism of AD, including abnormal tau metabolism, β -amyloid deposition, and inflammatory response. However, despite our deeper understanding of the pathological mechanisms of AD, effective treatments are still lacking. Therefore, the treatment strategies for AD have always been a hot and difficult point in medical research.

In recent years, passive immunization strategies for the β -amyloid hypothesis have become a new direction for AD treatment. Lecanemab is a monoclonal antibody against soluble A β fibrils that can quickly remove A β in the brain and slow down brain amyloid accumulation. In patients with early AD, Lecanemab treatment can significantly delay clinical deterioration and improve cognition and quality of life. However, the study has limitations. Long-term safety and efficacy data are insufficient and require more time and resources to invest in long-term clinical trials. Moreover, the association with other diseases such as Down syndrome has not been adequately studied. The optimal use method and dosage still need to be explored, and future directions include personalized treatment strategies. In conclusion, although Lecanemab demonstrates efficacy in AD treatment, more studies are needed to verify long-term safety and efficacy. Future research directions include large-scale clinical trials evaluating long-term efficacy and safety, and in combinations with other therapeutic approaches. With the development of medical research and technology, it is believed that more effective drugs will be available in the future to bring better treatment results and quality of life for AD patients.

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