Proceedings of the International Conference on Modern Medicine and Global Health (ICMMGH 2023)
DOI: 10.54254/2753-8818/6/20230198

Current drug treatments for Alzheimer's disease

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Abstract. Alzheimer's disease (AD) is one of the four biggest killers of the elderly, along with heart disease, lung cancer and cerebrovascular disease. However, the current understanding of the underlying causes and treatment of AD is based only on some hypotheses, which makes our research on AD urgent. Based on the common inducing hypotheses of Alzheimer's disease, such as β-amyloid deposition hypothesis, tau protein phosphorylation hypothesis, and viral infection hypothesis, this article will search and summarize a variety of specific drugs for different pathological hypotheses in the medical community, including those that have been marketed and those that have shown good therapeutic effects in clinical trials. Find, understand and analyze the advantages and disadvantages of each specific drug, so as to better and faster help to study the latest specific drug for Alzheimer's disease, and change the quality of life and physical condition of people with Alzheimer's disease and their families.

Keywords: specific drugs, tau protein, beta-amyloid, Alzheimer's disease, development.

1. Introduction

AD is one of the four leading killers of the elderly, along with heart disease, cancer and cerebrovascular disease. At present, the degree of population aging in China is gradually increasing, and the prevalence of Alzheimer's disease is also increasing. AD can lead to cognitive dysfunction, emotional disorders, mental disorders, and behavioral abnormalities. It causes irreversible damage to the patient's nerve cells. According to the data of 2021, the number of AD patients in China ranks first in the world. There are 5 million patients with AD in China, accounting for one quarter of the world's total, with an average of 300,000 thousand confirmed cases per year. Alzheimer's disease affects more women than men, and women over the age of 60 are usually two to three times more likely to develop the disease than matched men.

At present, the pathogenesis of AD is still controversial, and there are some hypotheses: β-amyloid hypothesis, tau hypothesis, cholinergic hypothesis, and metal ion disorder hypothesis. The drug treatment is mainly based on the development of β-amyloid and tau protein phosphorylation to target its pathogenesis

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2. Drugs for Alzheimer's disease

2.1. Drugs targeting beta-amyloid

The hypothesis of the pathogenesis of Aβ begins with the Aβ amyloid precursor protein being cleaved by β-secretase, which then produces insoluble Aβ fibers. Aβ oligomerization then diffuses into the synaptic cleft, forming insoluble starch fibers that aggregate into plaques. It made to hyperphosphorylation of tau protein, which produces microglia activation and local inflammatory response, and also facilitates the spread of neurotoxicity [1].

A human monoclonal antibody, ----Aducanumab (Biogen), has therapeutic efficacy by binding to β-amyloid and soluble oligomers. Drugs for the treatment of AD caused by the heap up of amyloid-beta (Aβ) protein. In an earlier study, a volunteer cohort of 165 patients with early-stage or mild AD who received monthly intravenous， 1 mg/kg, 3 mg/kg, 6 mg/kg, and · 10 mg/kg showed significant reductions in amyloid plaques in a dose-dependent and time-dependent manner, after 12 months, Nearly half of patients who received the 10 mg/kg did no longer had a positive amyloid PET scan [2].

Gantenerumab is a anti-Aβ monoclonal antibody, which can bind to Aβ protein and promote the clearance of aggregated Aβ protein through Fc receptor phagocytosis. In the phase III randomized trial of gantenerumab in early AD, 3089 patients aged 50 to 85 years were receive placebo every 4 weeks, 105 mg SC of gantenerumab every 4 weeks, and 10 mg SC of gantenerumab every 4 weeks. gantenerumab 225 mg SC. Patients with 0 or 1 APOEε4 allele were randomly assigned to either treatment arm, whereas APOEε4 homozygotes could only be assigned to placebo and gantenerumab 105 mg SC.

Finally, of 3089 patients, 25.9% patients were randomly assigned and receive at least one study-drug injections. At the time of the analysis, 316 patients had completed the 2 years of treatment. An additional 278 patients were enrolled and didn't complete 2 years of treatment and 203 patients gave up the treatment, most commonly because of adverse events, withdrawal of consent by themselves or a legal guardian, or initiation of symptomatic treatment. However, gantenerumab has been initiated and is currently undergoing phase 3 clinical trials [3].

In A phase 2 study of donanemab, a targeted, modified form of deposited Aβ antibody, 257 patients with the early symptomatic AD who were 60 to 85 years of age, randomly assigned in a 1:1 ratio to receive donanemab cure (700 mg for the first three doses, 700 mg for the first three cure and 700 mg for the second dose, every 4 weeks. Then 1400 mg) and placebo for up to 72 weeks. 131 patients were assigned to receive donanemab and 126 to receive placebo.

Ultimately, the change from ground line in the iADRS score at 76 weeks was the 6.86 points in the donanemab group and the 10.06 points in the placebo control group (difference is 3.20 < 0.05). 95% interval, 0.12-6.27 :P =0.04). At 76 weeks, there was a reduction in the amyloid plaque level and a greater reduction in the total tau load with donanemab than with placebo, and amyloid-related cerebral edema mostly asymptomatic occurred in patients who received donanemab. It also has good efficacy in early AD [4].

2.2. Drugs targeting tau

In the tau hypothesis, hyperphosphorylation of Tau leads to the pathogenesis of AD. When tau comes into contact with the released kinase, Tau is hyperphosphorylated due to the large amount of Aβ in the environment, resulting in its oligomerization. Because of the dissociation of tubular subunits, which cause the tubules to become unstable, these subunits break down, then transform to large chunks of tau filaments, which aggregate into NFTS. highly insoluble patches in the cytoplasm and processes of neurons, leading to abnormal loss of communication and signal processing between neurons, eventually neuronal apoptosis [1].

RO7105705, it is a humanized anti-tau monoclonal in development for AD, other neurodegenerative diseases. A phase I clinical trial has been completed in patients with mild AD and healthy people. A phase II clinical trial is under way [5].

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BIIB092 is a humanized IgG4 monoclonal Tau antibody that recognizes tau sequences and reduces free tau levels in the brain and spinal cord [6].

ABBV-8E12 is a monoclonal antibody developed for pathological tau aggregation and can recognize the N-terminal sequence of tau. Preliminary studies have shown that ABBV-8E12 can significantly reduce brain neurofibril pathology and insoluble Tau protein content in p301sTau mice. At present, it completed the phase I clinical trials，it also showed a good safety and tolerance [6].

2.3. The impact of antiviral drugs on Alzheimer's disease

In the pathogenesis of AD, it has also been suggested that it is caused by viral infection. Studies have shown that the viruses involved are herpes virus type 1-7, hepatitis C virus, and HIV, among which there are also some antiviral drugs that have been shown to be able to treat AD [7].

Penciclovir and foscarnet, the first one penciclovir is an antiviral drug, it used to treat various herpes virus infections. It is a DNA-specific polymerase inhibitor that is mainly used to treat herpesviridae infections. but in vitro studies showed that these both drugs inhibited the accumulation of amyloid-B, phosphorylated tau protein induced by HSV-1 infection in a concentration-dependent manner [7].

Pleconaril is an oral or intranasal antiviral drug, and ribavirin is an antiviral drug for the treatment of human respiratory syncytial virus infection, hepatitis C, and viral hemorrhagic fever. It has activity against viruses of the picornaviridae family. In a double blind, placebo controlled study of 69 patients who got mild AD who were treated with pleconaril and ribavirin found that the combination was poorly tolerated, the dropout rate was 50% due to ribavirin side effects. However, the overall clinical status deteriorated over time [7].

3. Summary

For the development of specific drugs for AD, scientists have studied the basic pathogenesis of AD, such as the accumulation of extracellular neuroinflammatory plaques formed by beta-amyloid, the hyperphosphorylation of tau protein formed by neuronal fibrillary tangles, synaptic damage and neurological dysfunction. From these hypotheses to explore and find the corresponding specific drugs to treat. However, many specific drugs proved to be ineffective in clinical trials, suggesting that there is uncertainty in drug development based on hypothesis. This uncertainty is that we have not really determined what is the pathogenesis of AD, but this is the limit of our current level of medical research, so we still need to learn more about the pathogenesis of Alzheimer's disease, Access to better technology can give patients more hope of being treated more effectively. Let's hope that more drugs can be found in the future development, so that Alzheimer's disease has a specific drug treatment.

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