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Analysis of drugs-based treatment methods for Alzheimer's disease

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Abstract. Alzheimer's disease (AD) treatment is one of the focuses of current medical research. Researchers have made progress in exploring the pathogenesis and treatment for AD, especially with disease-modifying therapies, cognitive enhancers, and medications for neuropsychiatric symptoms. However, there is still a research gap on how to effectively combine these drugs to improve the quality of life for AD patients. Therefore, this research aims to explore the effects of three drugs on AD, including lecanemab, brexpiprazole, and donepezil. This research systematically analyzed the efficacy of three drugs in different aspects of the disease: lecanemab as a disease-modifying therapy, brexpiprazole for relieving agitated symptoms, and donepezil for improving cognitive function. Through the analysis of their action mechanisms and clinical trial data, this research reveals the different roles of these drugs in AD treatment. The research results indicate that the combination of these three drugs can improve patients' symptoms from different aspects. Because of the various pathological mechanisms of AD, individualized multi-drug combination therapy may be an effective direction for future treatment.

Keywords: Alzheimer's disease; Drugs; Treatment methods.

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia, with symptoms typically including loss of short-term memory, language difficulties, self-care challenges, emotional instability, loss of motivation, and various other behavioral issues. At the pathological level, the accumulation of amyloid beta (Aβ) in the brain and neurofibrillary tangles composed of hyperphosphorylated tau protein are the main causes of AD, causing synaptic dysfunction and neuronal death [1].

Lecanemab can be used to reduce pathological progression and shows a good affinity for binding to soluble Aβ protofibrils. Therefore, it has been used to treat AD [2]. The trial further demonstrated lecanemab efficacy by predicting the relationship of plasma Aβ42/40 ratio and p-tau181 to brain amyloid, CDR-SB, and ADAS-Cog14 [3]. Brexpiprazole is a serotonin-dopamine activity modulat, and its efficacy, safety, and tolerability in treating AD have been analyzed [4]. According to the Cohen-Mansfield Agitation Inventory (CMAI) and Clinical Global Impression-Severity of illness (CGI-S) as related to agitation and safety, aripiprazole was also evaluated in treating AD for different aspects. Donepezil can be used to enhance cognitive function. A double-blind, multicentre, placebo-controlled clinical trial directly assessed whether donepezil improved cognitive function using data [5]. In another single-arm, prospective, multicentre trial, the efficacy of donepezil was again analyzed by MMSE, and the safety of donepezil was also analyzed by the incidence of adverse events [6].

This research will provide a detailed introduction to AD strategies based on different drugs, including disease correction therapy (DMT), neuropsychiatric symptom drugs, and cognitive enhancers. Specifically, the therapeutic mechanisms and effects of the three drugs for AD will be systematically discussed, including lecanemab, aripiprazole, and donepezil.

2. Lecanemab

2.1. Mechanism

As an amyloid-β-directed antibody, lecanemab is administered by intravenous infusion and is designed to block the pathological progression for AD. The core mechanism of lecanemab is to reduce the deposition of soluble Aβ protofibrils in the brain and prevent further Aβ aggregation by targeting soluble Aβ protofibrils [7]. Aβ protofibrils are a major contributor to the pathophysiology of AD, causing neurotoxicity through disruption of the electrophysiological systems responsible for memory function. Lecanemab shows a strong affinity for soluble Aβ protofibrils, with a binding capacity 100 times more than that of other anti-amyloid medications [7]. Through the mechanism, lecanemab effectively reduces pathogenic Aβ levels in the brain, showing therapeutic potential for AD in clinical trials.

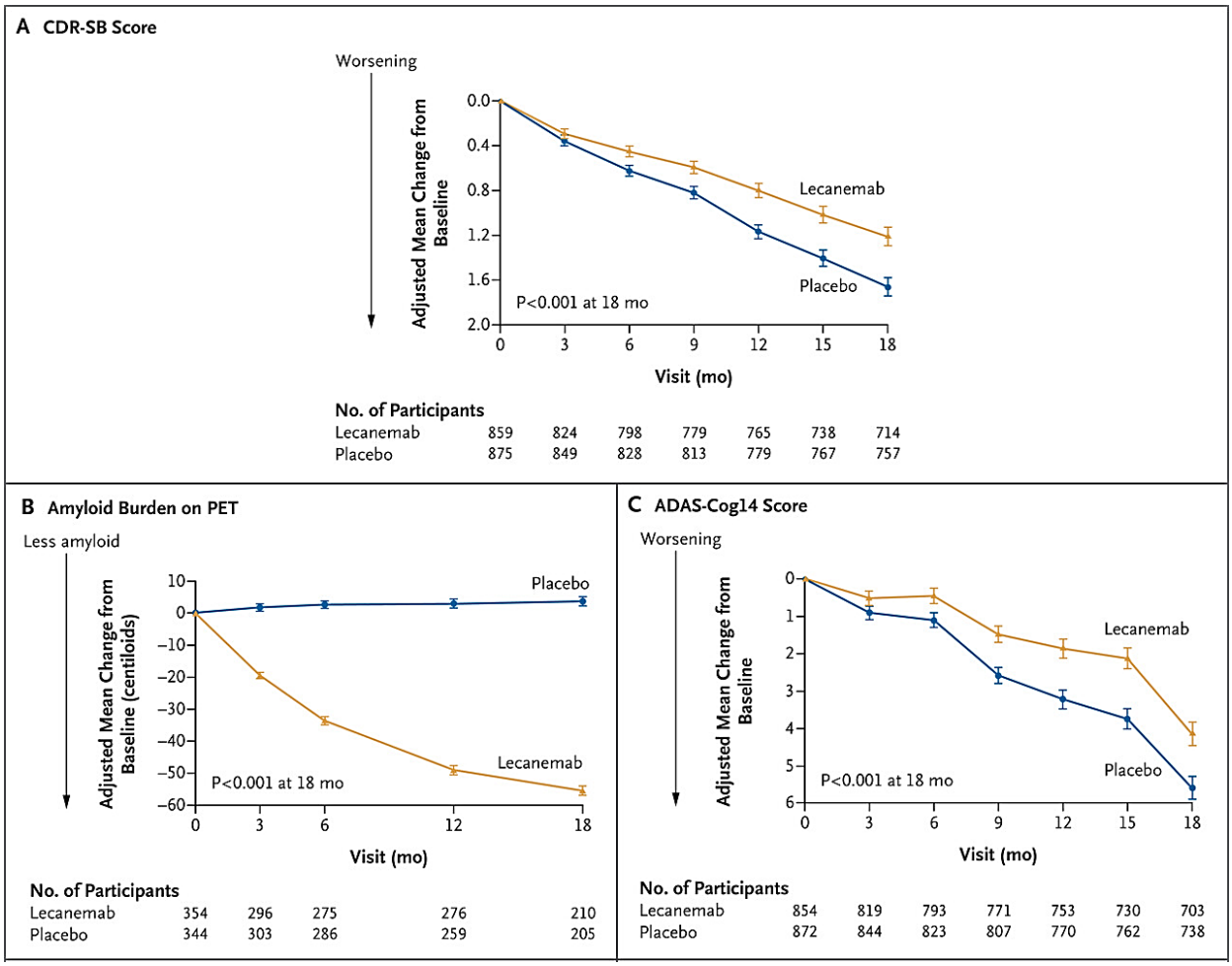

Figure 1. Data about the variation in different conditions [2]. (A) CDR-SB score. (B) PET's amyloid burden. (C) ADAS-Cog14.

2.2. Clinic trial

Lecanemab was evaluated in an 18-month, phase 3, multicenter, double-blind, placebo-controlled, parallel-group trial and analyzed primarily in terms of CDR-SB, changes in amyloid burden of PET and safety [2]. After 18 months of treatment, the change in the CDR-SB score of the lecanemab group was smaller than placebo, suggesting that lecanemab was more effective than placebo. Mean CDR-SB (higher scores reflecting more impairment) scores at baseline were approximately 3.2 in both the lecanemab and placebo group. Lecanemab group CDR-SB scores changed by an average of 1.21 at 18 months, while placebo group CDR-SB ratings changed by an average of 1.66. In addition, the use of lecanemab has a greater reduction in brain amyloid burden. In the PET study of amyloid burden,

the mean amyloid level in the lecanemab group was at 77.92 centiloids at baseline and was reduced to 22.44 centiloids in the lecanemab group. The mean amyloid level in the control group was at 75.03 centiloids at baseline and eventually changed to 78.67 centiloids. Lecanemab group ADAS-cog14 (higher scores reflecting more impairment) mean score at baseline was 24.45, adjusted to 28.59. In the placebo group, it changed from 24.37 to 29.95. However, lecanemab is thought to be associated with adverse events, with 14% of clinical trial participants experienced serious adverse events, compared to 11.3% in the placebo group. The most common serious adverse events include infusion-related reactions, ARIA-E and syncope, which led to discontinuation of medication in some participants.

Lecanemab treatment reduced amyloid deposition in the brain [3]. After 12 months of treatment, 65% of subjects went from amyloid-positive to amyloid-negative, and this increased to 81% at 18 months. In this clinical study, the reduction of amyloid treated with lecanemab showed a significant correlation with the reduction of decline in clinical assessments such as CDR-SB and ADCOMS. Meanwhile, plasma biomarker analysis demonstrated an increase in the Aβ42/40 ratio and a decrease in p-tau181 levels in plasma during lecanemab treatment. Ultimately, the study assessed the relationship between clinical efficacy endpoints and change from baseline of plasma biomarkers through model predictions, thus demonstrating that plasma biomarkers can serve as an important predictor of slowing cognitive decline. Model predictions indicated that a 0.25-unit improvement in the Aβ42/40 ratio corresponded to a 6.92% and 6.12% reduction in disease progression rates for CDR-SB and ADCOMS, respectively. As shown in Figure 1, a 0.1 pg/mL decrease in p-tau181 resulted in a 5.71%, 4.29%, and 5.78% reduction in disease progression rates for CDR-SB, ADCOMS, and ADAS-Cog14, respectively.

3. Brexpiprazole

3.1. Mechanism

Brexpiprazole has been studied in recent years for the treatment of agitation in AD patients [8]. The action mechanism for brexpiprazole is mainly through the regulation of serotonin, dopamine, and norepinephrine receptors [8]. It binds with high affinity to a variety of receptors. Specifically, brexpiprazole has a partial agonist effect on 5-HT1A and D2 receptors, and a potent antagonism on 5-HT2A, α1B, and α2C adrenergic receptors. Brexpiprazole has a lower intrinsic activity on the D2 receptor but a higher binding affinity for the 5-HT1A/2A receptor and therefore has a better antipsychotic potential while reducing side effects associated with D2 receptor agonists and antagonists [8]. Overall, brexpiprazole is a unique regulator of serotonin-dopamine activity that may provide new treatment options for a variety of central nervous system diseases.

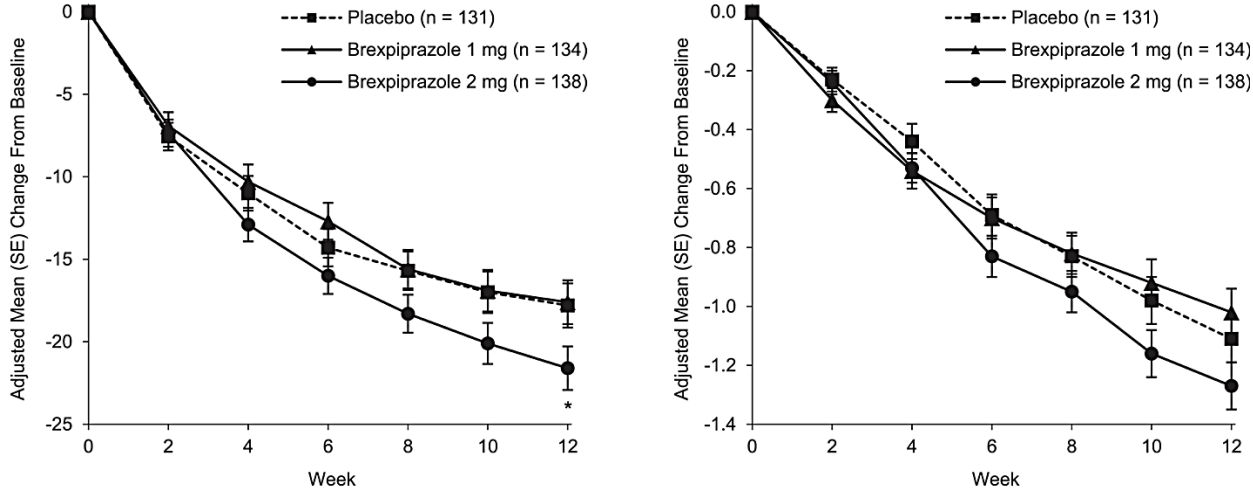

Figure 2. CMAI total score change (left) and CGI-S as related to agitation score change (right) [4].

3.2. Clinic trial

Two 12-week parallel-arm, randomized, double-blind, placebo-controlled studies provide new evidence for the treatment of brexpiprazole in AD [4]. The existing study showed a statistically obvious improvement in CMAI score in 2 mg brexpiprazole group (Figure 2). After 12 months of treatment, the adjusted mean changes from baseline in 2 mg brexpiprazole group, 1 mg brexpiprazole group, and placebo group were -21.6, -17.6, and -17.8, respectively. Changes in the CGI-S score associated to agitation revealed better improvement in 2 mg brexpiprazole group. The mean CGI-S score at baseline was 4.5 in 2 mg brexpiprazole group. After 12 months, adjusted mean change from the baseline of CGI-S score as related to agitation was -1.27, -1.02, and -1.11, respectively.

The existing study also showed an improvement in total CMAI scores compared to placebo in patients titrated to the maximum dose (2 mg) only at week 4, with no statistical advantage in the brexpiprazole 0.5-2 mg group. For the mean CGI-S score, brexpiprazole 0.5-2 mg and placebo baseline were both 4.5. After 12 months, the adjusted mean change from baseline was -1.32 and -1.02, respectively. At the same time, the assessment of safety and tolerability are also very important considerations for the development of new drugs. The groups receiving brexpiprazole 2 mg, 0.5-1 mg, and placebo had TEAE incidences of 65.0%, 49.0%, and 45.9%, respectively. Nonetheless, the majority of TEAEs were mild or moderate in intensity, with headaches, insomnia, dizziness, and urinary tract infections accounting for ≥5% of TEAEs in 2 mg brexpiprazole participants. There were no deaths associated with brexpiprazole treatment. Overall, 0.5-2 mg of brexpiprazole is both secure and well tolerated in Alzheimer's patients.

4. Donepezil

4.1. Mechanism

Donepezil can be used to improve cognitive function in AD patients. Donepezil prevents acetylcholine hydrolysis by reversibly binding to acetylcholinesterase and thus increases levels of the neurotransmitter acetylcholine [9]. People with AD often have low levels of acetylcholine in their brains, which plays an important role in nerve conduction in the brain related to memory, learning, and attention. Donepezil enhances neural signaling and improves cognitive function by reducing the breakdown of acetylcholine and extending the presence of acetylcholine in the synaptic gap. In addition to raising acetylcholine levels by inhibiting acetylcholinesterase, donepezil has other neuroprotective effects, such as antagonizing glutamate-induced excitotoxicity and affecting amyloid processing and deposition, and these effects more directly affect the pathophysiology of AD [9].

4.2. Clinic trial

A multicenter, double-blind, placebo-controlled clinical trial was conducted to evaluate the effect of donepezil on AD [5]. The results of this trial showed that continuous use of donepezil significantly improved cognitive function during the 12 months of treatment. Patients treated with donepezil for 52 weeks had, on average, 1.9 points higher SMMSE (indicating improved cognitive function) and 3.0 points lower BADLS (indicating less dysfunction) than those who discontinued donepezil. The experiment showed that over time, the effect of treatment was more significant, from an average increase of 1.0 points at week 6 to an average increase of 1.9 points at week 52. The experiment also studied memantine, the effect of memantine treatment is not as significant as donepezil. Patients treated with memantine for 52 weeks had, on average, 1.2 points higher SMMSE value and 1.5 points lower BADLS value than those who stopped memantine therapy, both of which were less than the minimum clinically important difference.

In a single-arm, prospective, multicenter trial, the safety of donepezil in AD patients was evaluated by incidence of adverse events (AEs) [6]. Donepezil 10 mg/day was found to be well tolerated in patients with mild to moderate AD. During the course of the trial, 156 AEs were reported, the majority of which had low or moderate severity (82.69% low, 14.74% moderate, and 2.56% severe). In >2%

of patients, diarrhea (5.39%), nausea (3.32%), and vomiting (2.9%) were the most frequent donepezil-related adverse events. Syncope, falls, or deaths did not occur. The trial also reported data from a Mini-mental State Examination (MMSE), where patients treated with donepezil 10 mg/day showed significant improvements in MMSE. The full analysis set (FAS) (actual data) of donepezil 10 mg/day MMSE was 18.69 at baseline, with a mean change of 0.97 from baseline after 20 weeks of treatment (indicating improved cognitive function). Repeated measurement analysis based on a mixed model found that age had a statistically significant effect on baseline MMSE change. In the treatment of donepezil 10 mg/day, patients younger than 75 years responded better than patients older than 75 years.

5. Comparative analysis

After analyzing the pathological mechanisms, neuropsychiatric symptoms, and cognitive function of lecanemab, brexpiprazole, and donepezil, respectively, the results show that the mechanism of action, efficacy, and safety of these three drugs have their advantages and disadvantages.

The mechanisms of action of these three drugs reflect different paths and goals in the treatment of AD. Lecanemab, as an antibody drug that primarily targets Aβ in AD pathology, directly intervenes in the pathological process by binding soluble Aβ fibril with high affinity and reducing its deposition in the brain, thereby potentially slowing disease progression. In contrast, donepezil increases levels of the neurotransmitter acetylcholine by inhibiting acetylcholinesterase, with a focus on improving cognitive function without directly affecting the pathological mechanisms of the disease. Brexpiprazole, on the other hand, is primarily used to relieve neuropsychiatric symptoms in AD by modulating neurotransmitter receptors such as 5-HT1A, 5-HT2A, and D2, acting on the dopamine and serotonin systems in a different mechanism than lecanemab and donepezil.

In the experiment, lecanemab showed a significant reduction in the level of amyloid burden. Both CDR-SB and ADAS-cog14 data also showed better efficacy than placebo. The Aβ42/40 ratio in plasma was inversely proportional to the CDR-SB value, while the p-tau181 value was proportional to the CDR-SB and ADAS-cog14 data. The plasma Aβ42/40 ratio improved whereas p-tau181 levels reduced. Research shows that lecanemab has great potential for disease-modifying therapies. However adverse effects in clinical trials, such as ARIA-E, have limited its use in a wide range of patients, requiring longer and more trials.

For the experimental study of brexpiprazole, 2 mg brexpiprazole showed a statistically significant improvement. A greater improvement than placebo was also shown on the CGI-S score associated with the activation of a secondary efficacy endpoint. Furthermore, studies have shown that brexpiprazole 0.5-2 mg is safe and well tolerated in AD patients.

Both the improved SMME and the reduced BADLS showed that donepezil was effective. The adverse events at donepezil could be mild or moderate, and no syncope, fall, or death occurred. According to studies, 10 mg/day donepezil offers some improvement in cognitive performance and is well tolerated.

Overall, the combination of these three drugs may provide a more comprehensive treatment option for AD. However, how to balance drugs to reduce adverse reactions, delay the disease, and improve the quality of the patients' life is still a problem to be solved. Future research not only needs to further evaluate the long-term efficacy of different drugs, but also explore the optimal strategy for multi drug combination therapy to maximize treatment effectiveness.

6. Conclusion

The treatment of AD can be started from three aspects: disease-modifying therapy, neuropsychiatric symptom drugs, and cognitive enhancers. Lecanemab, as a disease-modifying therapy, can effectively reduce the accumulation of amyloid plaques, thereby delaying the progression of the disease. Brexpiprazole is primarily used to relieve agitated symptoms and improve mood and behavior in patients. Donepezil is a cognitive enhancer that boosts neurotransmitter levels by inhibiting

acetylcholinesterase, helping patients improve cognitive function. Therefore, targeting the multiple pathological mechanisms of AD, the use of different drug combinations is expected to improve the therapeutic effect. In summary, lecanemab showed potential in slowing the progression of pathology, while brexpiprazole and donepezil showed some efficacy in improving neuropsychiatric symptoms and cognitive function, respectively. It is suggested that the appropriate treatment plan or combination of drugs can be selected according to the specific symptoms of patients in clinical practice. The possible reason is that the complex pathological mechanism of AD requires multi-faceted intervention. This research can be used to reveal the potential role of drugs with three different treatment strategies in AD, which is conducive to the subsequent study of the combined use of drugs. For future studies, it is recommended to further explore the long-term efficacy and combined use of drugs.

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