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A Drug for Alzheimer's Disease: Aducanumab

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Abstract. Alzheimer's disease (AD) is a problem that has plagued humans for a long time. About 24.3 million people have Alzheimer's disease in the world, and the number is growing at a rate of 4.6 million new patients each year. The prevalence of AD increases with age. As a result, the issue of AD has become increasingly negative in recent years. The purpose of the paper is to examine whether the marketed aducanumab is useful in the treatment of AD and to compare it with several other drugs commonly used to treat AD. This paper will discuss the effectiveness and adverse effects of common medications for AD treatment and why aducanumab has not been effective in treating AD and how to improve the effectiveness of aducanumab for AD patients in the future. In addition, this paper will analyze whether aducanumab is marketed because of commercial considerations or because the drug itself was fully compliant with FDA requirements.

Keywords: Alzheimer’s Disease, Aducanumab, Cholinesterase Inhibitor, N-Methyl Dimethyl Receptor Antagonist.

1. Introduction

Alzheimer's disease (AD) is a degenerative disease of nervous system. Alzheimer's disease is very painful for those who suffer from it and their families. Clinical manifestations of AD include memory loss, reduced language and motor skills, personality changes, disorientation and intermittent inappropriate behavior. As a result, patients often fail to remember who they are and forget the familiar people around them. The cause of AD is still unclear, but the one that is well recognized is by a large amount of β-amyloid protein (Aβ) deposited in the brain. There are also no medications that can completely treat AD, but there are some medications that have been shown to reduce the manifestations of AD.

In recent years, there are many different treatments for Alzheimer's disease including medication, other interventions, among which medication is the most commonly used method. However, there are not yet sufficiently effective drugs to cure it. These include drugs that act on neurotransmitters, such as cholinesterase inhibitors and N-methyldimethyl receptor antagonists. In addition to the above-mentioned drugs, aducanumab is another medicine that has been recently approved by the US Food and Drug Administration (FDA). However, the approval of aducanumab is quite controversial as some pharmacologists question its efficacy.

This paper, aims to introduce several common drugs for AD treatment and explore why some pharmacologists think that aducanumab is not an ideal drug by comparing with other current main drugs. Specifically, the experimental data and effects of cholinesterase inhibitors, N-methyldimethyl

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antagonist, and aducanumab will be collected to help analyze aducanumab as the first target medicine of biomarker with Alzheimer's disease.

2. Cholinesterase inhibitor

Cholinesterase inhibitor has been one of the most popular medicines in treating AD in the past 10 years. Tacrine is a central cholinesterase inhibitor, which has additional pharmacological activities on monoamine level and ion channels. Its mechanism of action is inhibiting cholinesterase and increasing the content of acetylcholine acetate in brain. The role of acetylcholine is that the main function is to maintain consciousness and thus relieve AD. The mechanism of this medicine is to reduce cholinesterase, because cholinesterase can destroy acetylcholine, which is a neurotransmitter, reducing neurotransmitters will lead to slow thinking. Therefore, it is possible to increase neurotransmitter transmission by disrupting cholinesterase, thus achieving dementia relief. Although this logic is correct, the harm of this drug to human body is enormous. It has side effects such as vomiting, diarrhea, myalgia, anorexia and rhinitis [1]. Alzheimer's disease, as a neurodegenerative disease, will not lead to people's death, and most of these patients with AD die from complications of AD. It can be seen that the side effects of these drugs are probably one of the reasons that aggravate the complications of AD [2].

3. N-methyl dimethyl receptor antagonist

Secondly, another widely used drug for treating AD is N-methyl dimethyl antagonist. Among them, N-methyl-d-aspartate receptor (NMDAR) is a major excitatory neurotransmitter receptor in human brain. It can regulate the variability in the brain, reshape synapses and change the functional structure of the brain. For treating AD, stimulating glutathione neurotransmission through NMDAR is essential for synaptic plasticity and neuron survival. However, excitability will result from excessive NMDAR, and thus promote cell death, which is the basis of the underlying mechanism of neurodegeneration in AD. The results suggest that the significant effects of NMDAR-mediated responses can be attributed for regional receptor activity, followed by various downstream signaling pathways. Activation of synaptic NMDARs can trigger plasticity and at the same time, lead to cell survival promotion. Conversely, activation of supersynaptic NMDARs may promote cell death, leading to AD development. NMDA can block the etiology of Alzheimer's disease and have therapeutic effects [3]. Physiological side effects of methamphetamine include: loss of appetite, psychomotor excitement, headache, arrhythmia (which may be tachycardia or bradycardia), shortness of breath, hypertension or hypotension, hyperthermia, diarrhea or constipation, blurred vision, dizziness, trembling, acne, etc. [4]. The function and mechanism of this drug are almost the same as those of cholinesterase inhibitors, except that the former acts on neurotransmitters, while this drug targets neurotransmitter receptors. Similarly, the use of this drug may also lead to the same results ： there are many side effects, yet the actual cure is not very effective.

4. Aducanumab

According to the effects of these two drugs, they are not the best drugs to treat AD, and long-term use of these two drugs will lead to many dangerous side effects. As a newly developed drug for treating AD, aducanumab represents a further understanding. It has been observed that AD is characterized by the deposition of A β -plaques and neurofibrillary tangles in the brain with synaptic dysfunction and neurodegeneration. In the transgenic mouse model of AD, Aduna monoclonal antibody enters the brain and reduces soluble and insoluble Aβ. However, the data obtained by them support the further development of aducanumab as an AD therapy to remove Aβ and improve diseases, because 3, 6 and 10 mg kg -1 doses of aducanumab significantly reduced amyloid positron emission tomography standardized uptake value ratio. In one year after the end of the treatment, the participants who took placebo and aducanumab all experienced a remission. Thus, the clinical and preclinical data provide sufficient and strong evidence for the continued development of aducanumab for the treatment of AD. The clinical research results also support for the biological hypothesis that aducanumab therapy can

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reduce brain Aβ plaque. Furthermore, it provides strong support for the clinical hypothesis that Aβ plaque reduction brings clinical benefits [5]. The support of aducanumab as a good clinical trial for the treatment of AD mentioned here refers to the phase II trial, not the expected phase III trial. Therefore, even if there are some clinical or preclinical supports, they cannot be substantial evidence.

To solve the problem that there is no effective drug to treat Alzheimer's patients, in 2021, FDA approved the marketing of aducanumab. Biogen, the company that makes Aduna monoclonal antibody, claims that aducanumab is a monoclonal antibody that targets the formation of amyloid plaques, which are thought to exacerbate AD. The drug is the first to treat the disease process, not just the symptoms. It is the first Alzheimer's drug to be approved in nearly two decades, and one of the few to be approved after FDA's expert advisory panel roundly rejected it [6]. However, this drug still faces a similar situation with other drugs for treating Alzheimer's disease. According to Biogen's statement, it can be concluded that aducanumab is a drug developed according to part of the pathogenesis of Alzheimer's disease, but it remains unknown how effective it is to treat AD. In the face of these doubts, the best way to stop messages is to produce data and evidence, but none of this is reflected in Biogen's statement. These are the things they avoid doing. They divert attention from the side effects and efficacy of aducanumab to the mechanism of the treatment drug.

Obviously, the therapeutic effect of this drug is not obvious, but there is still much room for improvement. Although aducanumab is the first drug to treat amyloid plaques in the brains of patients which has been approved by FDA, the public still has many doubts about it. Duke Health, as one of the most authoritative medical research centers, claimed that FDA approval of Aducanumab is controversial. Clinical trials examining its efficacy have not shown cognitive performance improvement. Two trials were even terminated prematurely for there was no clinical benefit that could be demonstrated [7]. This means that Biogen has not succeeded in diverting attention, even though they issued a statement intended to convince people that the drug was fully compliant with the marketing criteria. Duke Health does not admit it. Besides, Duke Health has decided not to make aducanumab available for the treatment of AD. For the questions raised by Duke Health, the listing of aducanumab is not that simple. The marketing of drugs is very strict. In addition to developing the drug, three phases of experimental research are needed, and a lot of procedures are also necessary before it can be successfully marketed. How aducanumab went on the market successfully without good results in Phase III trial is a question that exists in the minds of many scientists. It is assumed that besides the purpose of science and treating patients, there is also commercial consideration. The research and development of a drug is very time-consuming and costly. Sometimes, when the phase III trial fails or gets stuck in the last procedure, the entire drug research and development team loses millions or even hundreds of millions of dollars. According to the evidence presented by Duke Health and other drug research institutes and Biogen's statement, many people have to believe that there is a capitalist conspiracy behind it.

Nevertheless, FDA does not agree with these statement and doubts. FDA said that they approved a new drug based on a biomarker, and amyloid in the brain is the biomarker of AD. Aducanumab has been shown in experiments to reduce cerebral amyloid plaques in Alzheimer's disease patients, which is a substitute for clinical benefits [8]. This kind of statement is not very beneficial. It is well known that there are three stages in drug experiment. The first stage is animal experiment, the second stage is experiment on a few volunteers, and the third stage is experiment and observation on more people. As mentioned in the previous introduction of Aducanumab, Aducanumab did significantly help Alzheimer's patients improve their memory in phase II trials, but it is not the case in phase III.

As stated by FDA, Aducanumab can reduce the accumulation of Aβ in brain. However, articles about Aducanumab rarely mention its therapeutic effect and some other side effects. In Selkoe's research, it can be seen that the patients who took placebo improved to some extent, and the patients who took Aducanumab improved more than those who took placebo. However, if psychological factors are excluded, the therapeutic effect of Aducanumab is very limited. That is to say, aducanumab was not successful. The data obtained by the researchers are not enough to support the listing of adunatumab [5].

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According to the research, the side effects of aducanumab are still obvious. From the experiments of the first two stages of aducanumab, it is indeed somewhat effective, as Selkoe mentioned. The β-amyloid protein in the brain of patients is decreasing. The more they use, the faster it will decrease. However, the more the dosage is, the greater the side effects will be, such as headache, urinary tract infection and upper respiratory tract infection. If a patient wants to make the therapeutic effect more effective, he/she can only increase the dosage. However, the increase of the dosage also means that the side effects will be aggravated. Side effects are also an important cause of complications in patients with AD. In scanning imaging of beta-amyloid in the brain, red would represent more precipitation and blue would represent less precipitation. The red portion of the patient's brain imaging gradually disappeared over the course of a year as the amount of medication was increased.

Medical Officer Jeff Sevigny and his team pointed out that if Aducanumab can still have the same effect as in phase I and phase II experiments in phase III experiment, then this drug is successful [9]. Although Aducanumab has a good therapeutic effect in the phase III trial, its side effects are still great. If that is the case, compared with the other two drugs, they are essentially the same, both of which can slow down slightly but have serious side effects. About 40% of patients at an early stage treated with Aduhelm in Phase III trial were found with a side effect of amyloid-related imaging abnormalities. Approximately 1/4 patients suffered these symptoms [10]. These numbers are quite alarming. The percentage of people who get side effects is not only high, but the severity of the side effects is also tremendous.

By analyzing the phase III trial, not surprising, the result is not as predicted by Jeff Sevigny's team. Robert Howard and Kathy Y. Liu claimed that ENGAGE is a Phase III trial of aducanumab, in which patients with early-stage AD are participating. The experiment was forced to be discontinued in March 2019. The reason for this is that the chance of finding a therapeutic effect of the drug through data analysis is small [11]. Therefore, the phase III clinical trial of Aducanumab cannot cure AD, but it does not mean that the laboratory failed. The emergence of effective treatment to slow down the progress will be an important milestone, but the listing of aducanumab is a commercial consideration for Biogen Company, rather than a consideration for treating Alzheimer's disease after the drug is completely successful.

5. Discussion

In conclusion, the therapeutic effect of aducanumab, cholinesterase inhibitor, and N-methyldimethyl antagonist are not ideal. They can only slightly slow down Alzheimer's disease, but they cannot achieve the complete therapeutic effect. At the same time, they all have very serious side effects, and the direct side effects will aggravate other complications of Alzheimer's disease. However, compared with the other two drugs, aducanumab has the lowest reliability, so all the data at present show that aducanumab did not achieve the expected therapeutic effect in the third phase experiment. The FDA does not strictly control the listing of aducanumab, so it is very possible that the listing of aducanumab is the commercial and economic consideration of Biogen Company. The discontinuation of aducanumab by Duke Health can better illustrate the problems in the research and use of aducanumab.

However, this may not be the case either. Matthew Schrag found that the images in Sylvain Lesné's paper had been modified. And it is Professor Sylvain Lesné's research that supports the idea that the mechanism of AD is the accumulation of Aβ in the brain. Therefore, from what we can see, the aducanumab is not very effective and most likely is itself wrong from the mechanism. Therefore, the research on Alzheimer's disease may have to be set back by a decade or so [12].

All the results show that aducanumab is an undesirable drug, the research and use of aducanumab still need further research. All the subjects of aducanumab are patients who already have AD. According to the mechanism of AD, patients will only get sick at the age of 60, but at the age of 40, the Aβ in the brain has been pushed up differently from ordinary people. Therefore, the damage of Aβ to the brain may be permanent, if the content of Aβ in the patient's brain is checked at the age of 40 and the treatment with aducanumab is started. In this way, the accumulation of Aβ in the brain can be reduced in time to avoid its permanent damage to the brain, and thus maybe aducanumab will have a

very obvious effect. Moreover, because the patient is young and has not yet developed the disease, he/she can also take aducanumab in a small number of times to reduce the risk of aggravation of side effects. Yong Ping, a researcher at Shanghai Jiaotong University, also talked about this conjecture in his sleep disorder and nervous system disease research class, which is very consistent with many other scientists. However, this experiment may take several decades, so there is no literature and data available for reference at present.

6. Conclusion

This article analyzes the therapeutic efficacy of the three main drugs currently commercially available for the treatment of AD by introducing Cholinesterase inhibitor, N-methyl dimethyl receptor antagonist, and aducanumab. Aducanumab, a drug based on the mechanism of AD, is supposed to be effective in treating AD, but it is as ineffective as the other two drugs. There are two possible reasons for this: the first is the ability of the drug to be marketed for commercial use, and the second is due to the mechanism of AD pathogenesis, which may be incorrect. Although there is no effective medication for AD at the moment, it is believed that in the near future it will eventually appear and help more families to solve their difficulties. This paper provides two directions for drug research in AD, the first is to change the timeline of aducanumab drug trials. The second is to re-examine the pathogenic mechanism of AD.

References

[1] A.J. Wagstaff, D. McTavish. Tacrine. A Review of Its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Alzheimer's Disease. Drugs & aging. U.S. National Library of Medicine, 4, 510-540 (1994).

[2] “Why Do People Die from Alzheimer's Disease?” How Do People Die From Alzheimer's Disease? https://www.agingcare.com/articles/why-do-people-die-from-alzheimers-disease-133297.htm. (Accessed 4 October 2022).

[3] R. Wang, P.H. Reddy. Role of Glutamate and NMDA Receptors in Alzheimer's Disease. Journal of Alzheimer's disease 57, 1041-1048 (2017).

[4] FDA. Methamphetamine Side Effects: Common, Severe, Long Term. https://www.drugs.com/sfx/methamphetamine-side-effects.html. (Accessed 4 October 2022).

[5] D. J. Selkoe. Alzheimer Disease and Aducanumab: Adjusting Our Approach. Nature Reviews Neurology 15, 365-366 (2019).

[6] Biogen's Aducanumab Crosses FDA Finish Line Just in Time to Save Its Business. https://www.fiercepharma.com/pharma/biogen-fda-aducanumab-decision. (Accessed 4 October 2022).

[7] Hull Erin, Morgan deBlecourt. “What You Need to Know about Aducanumab.” https://www.dukehealth.org/blog/what-you-need-know-about-aducanumab. (Accessed 4 October 2022).

[8] Talan, Jamie. “Dementia Experts on Why the FDA Approval of Aducanumab for Alzheimer's Gets Mixed Grades” https://journals.lww.com/neurotodayonline/fulltext/2021/07080/dementia_experts_on_why_the_fda_approval_of.3.aspx. (Accessed 4 October 2022).

[9] Sevigny, J., Chiao, P., Bussière, T. et al. The antibody aducanumab reduces Aβ plaques in Alzheimer’s disease. Nature 537, 50–56 (2016).

[10] Kansteiner Fraiser. Aria Side Effects Surface in 40% of Patients on Biogen's Alzheimer's Drug Aduhelm: Jama. https://www.fiercepharma.com/pharma/aria-side-effects-surface-40-patients-biogen-s-alzheimer-s-drug-aduhelm-jama. (Accessed 4 October 2022).

[11] Howard, R., Liu, K.Y. Questions EMERGE as Biogen claims aducanumab turnaround. Nat Rev Neurol 16, 63–64 (2020).

DOI: 10.54254/2753-8818/4/20220625

[12] Newsdesk Benzinga. Potential Fabrication in Research Images Threatens Key Theory of Alzheimer's Disease -Science.org Report https://www.benzinga.com/news/22/07/28158910/potential-fabrication-in-research-images-threatens-key-theory-of-alzheimers-disease-science-org-repo. (Accessed 4 October 2022).