Aducanumab - a potential pharmacological therapeutic treatments for Alzheimer's disease

Chen Ding *

University of Toronto Scarborough, Toronto, Canada

* Corresponding author: annychen.ding@mail.utoronto.ca

Abstract. The first cause of dementia symptoms in the elderly worldwide is Alzheimer's disease (AD), which lead to a continuous and gradual memory loss that causes significant distress towards people. Known from World Alzheimer's Report, dementia is now the top 7 mortality cause globally. There are several hypothesis of AD pathogenesis. Among them, beta-amyloid cascade hypothesis and hyperphosphorylation of tau protein are two of the most mainstream opinions. However, beta-amyloid cascade hypothesis is being questioned. In order to deal with this disease, both non-pharmacological (cognitive improvement) and pharmacological therapeutics (rivastigmine) can relieve symptoms of AD, such as dementia to some extent, but they cannot directly treat AD. Under this situation, for the purpose of finding drugs that can cure AD, thousands of drugs clinical trials are under progress. Although most of the ongoing drugs passed through the phase 2 clinical trial successfully, only Aducanumab passed though the phase 3, becoming the first new drug for AD approved by FDA. Nonetheless, Aducanumab is controversial in the scientific community. This paper briefly introduces the mechanism of action and research progress of aducanumab.

Keywords: Alzheimer's disease, Aducanumab, Mechanism, Pathogenesis.

1. Introduction

Globally, the impact of Alzheimer's disease (AD) on families and economies is enormous. As the audit slowly ages, so does the neuron or brain. The typical manifestation is dementia. As the name suggests, AD not only impairs the patient's ability to exercise, but also makes them unable to take care of themselves. Moreover, the cognitive impairment is even more unacceptable. This can lead to severe mental and memory deterioration. However, although researchers have been studying AD for a long time. Related progress is still limited. A degenerative neurologic illness called Alzheimer's disease (AD) has a mechanism that involves the buildup of Abeta and the initiation of secondary processes (e.g., tau hyperphosphorylation). Beyond the age of 65, it coincides with memory loss figuratively. There would be 5.8 million Americans living with AD by the end of 2020. Age and genetic predisposition are just two of the several risk factors. AD can often be divided into two categories: sporadic and familial. Sporadic AD, often known as late-onset AD (LOAD), typically affects adults over 65. Early-onset AD is the term for familial forms, which happen in people aged 30-65 and are impacted by genetic and inherited factors. Some genes, such as APP, PSEN1, and PSEN2, are where the familial type of AD is thought to have its origins. Most occurrences of AD are sporadic and are caused by environmental circumstances, with only a small amount of genetic involvement.

Formerly, researchers used to employ expensive and challenging medical imaging procedures to diagnose AD. As a result, researchers have discovered two cutting-edge techniques in recent years to diagnose AD. LRRGD is first utilized to recognize AD proteins. In the end, 376 proteins are discovered to be connected to AD, aiding in the diagnosis of AD. Additionally, spectrogram characteristics from voice data were retrieved to indicate AD. This can detect AD early on so that people can take preventative measures [1].

Despite ongoing debate, the FDA recently approved aducanumab in nearly 20 years, regarding the anti-AD medications, the first brand-new treatment for AD. There have been more than 25 unsuccessful clinical studies trying drugs for the treatment of AD in the past. Two pre-approval phase III trials with identical designs should have provided a solution, but they did not. Both trials were terminated after early evaluations of the data collected up until December 2018 revealed that they were

"futile" (with a 20% likelihood that the whole study would result in a positive finding) [2]. Nevertheless, the trial's financier, Biogen continued to gather data up to the announcement of its cancellation in March 2019. The ineffectiveness of the medicine was confirmed by the reanalysis of data through March 2019 in one research, but cognitive improvement was suggested by the other [2]. This essay discusses the pathogenesis of AD, several potential medication treatments, and the contentiousness of the medicine - Aducanumab.

2. hypothesis of AD pathogenesis

In fact, the specific mechanism of the pathogenesis of AD has not been deciphered by scientists yet due to its complexity. However, researchers have proposed several hypotheses of AD pathogenesis in order to struggle with this complicated disease. First, professors thought the accumulation of β-amyloid peptides in plaques and vessel walls was the leading item in the pathogenesis of AD [3]. Along with the catalysis by α, β, and γ-secretases, the endoproteolysis of β-amyloid precursor protein (APP) takes place. In the beta-secretase pathway, beta-amyloid peptides: Abeta 40 and 42 are generated. Most known APP and progeria protein mutations affect APP processing, leading to overproduction of Abeta, which contains neurotoxicity and stronger hydrophobicity compared to Abeta 40. Therefore, neurodegeneration occurs. Second, aggregation of tau protein, which is abnormally-phosphorylated, is another major pathological event [4]. Hyperphosphorylation of tau protein may modulate the conformation and charge of proteins. Additionally, through the self-assembly of tau protein, paired helical filaments (PHFs) are produced, which will lose the MT stability and are found to be potential neurotoxins. Third, dysfunction of mitochondria can also be causation of AD [5]. DLST of the mitochondrial Krebs cycle and ALDH2 are related to AD. MIRTD, one of the gene products of DLST, make a difference in the process of molecular assembly of cytochrome c-oxidase complexes, whose decline influences the production of power, so that its defect has become candidate genes that cause AD. ALDH2 is considered to be a protector of oxidative stress. Hence, the decrease in the activity of ALDH2 is thought to be one of the causes of AD. Fourth, the cholinergic hypothesis of AD is one of the earliest theories about the performance of AD. The severity of Alzheimer's dementia is discovered to be positively correlated with the degree of cholinergic loss [6]. Furthermore, in the very early stages of AD, neurofibrillary degeneration of the cholinergic NbM neurons (Ch4) is present, even until the pre-stage of cell death, which is linked to cognitive deficits. Among these hypotheses of AD pathogenesis, the majority of people proposes that the deposition of Abeta and Tau protein are two main causes. Apart from the above, other circumstances, such as inflammation and autophagic lysosomal pathway, are factors that affect AD by influencing Abeta and tau protein.

However, recently, the function and even the existence of Abeta 56 has been doubted by Matthew Schrag. In the paper of Sylvain Lesné in 2006, he supposed that Abeta 56 was closely associated with memory. When Abeta 56 was injected into the mice, their recall of simple and previously learned information was dramatically reduced. This academic fraud has greatly impacted research of therapeutic targeting Abeta.

From the controversial β-amyloid peptide hypothesis to tau protein precipitation, as well as the growing number of studies on mitochondrial dysfunction and the cholinergic hypothesis, the possible mechanisms of AD are explained from different perspectives. However, related disputes are also increasing. With the advancement of diagnostic technology, detection of neuronal electrical activity, and high-throughput genetic assays, AD research can be well promoted. The discovery of therapeutic mechanisms and pathophysiology could further advance the therapeutic approach. At present, precision medicine is gradually entering clinical practice. High-tech information technology has entered the intervention treatment method. For AD, perhaps the most important thing is to further explore its essential pathogenesis and correctly intervene in the risk factors in the progression of the disease, which is the hope of potential treatment in the future.

3. The Treatment of Ad

There are two categories of therapies for AD: non-pharmacological and pharmacological. Speaking to non-pharmacological therapies (NPTs) [7]. In dementia patients, NPT improves behavioral issues and cognitive abilities [8]. In traditional treatment, it is believed that exercise and exercise rehabilitation can promote the improvement of AD symptoms to a certain extent. Cognitive rehabilitation, psychotherapy, etc., also have a good effect on delaying the decline of cognitive ability of AD patients, helping patients adapt to family life, and reducing premature dependence on nursing staff for service treatment. In recent years, new intervention technologies have emerged, such as information and communication technology, assistive technology and family medicine, virtual reality, games, and telemedicine, which can quickly and conveniently help patients receive consultation and treatment earlier and in a timely manner. Individualized treatment is also possible. The methods briefly mentioned above are the main types of NPT, and many other new treatments are not introduced here due to space limitations. Other NPT types include occupational therapy and psychological therapy [9]. For several months, NPTs were administered to 21 patients with dementia in Shigihara Y's observational study. By using the MMSE-J and a condensed version of the Dementia Behaviour Disturbance Scale (DBD-13) to assess cognitive abilities and behavioral disorders at the start and the conclusion of the NPT period, the average MMSE-J score rose after the NPT period, in contrast to the average DBD-13 score (detection of sensorimotor area beta activation). This confirms that NPT has an impact on participants' and dementia-at-risk individuals' brain activity. In addition, the results provide more proof that dementia sufferers' brains are capable of plasticity, which may be the cause of the NPT effects that have been noticed. NPT might enhance the quality of life in dementia patients [9].

Turning to pharmacological therapies, almost all FDA-approved therapies are symptomatic, which slows the progression of AD [10]. These therapies are divided into three classes: Cholinesterase inhibitors, which act by inhibiting the neurotransmitter, are the first group of drugs. In addition, NMDA receptor antagonists are the second class of drugs. The combination therapy currently advocated by many researchers is the third therapy. The purpose of cholinesterase inhibitors is to increase the level of ACh, and these inhibitors can increase Ach in the brain. Typically, the function of NMDA receptors is to permit Ca2+ ions to enter the neurotransmission. Nevertheless, in the case of AD, the NMDA receptor exhibits high activity, causing too many calcium ions to enter the nerve, which leads to excitatory toxicity and cell death. Memantine, an NMDA receptor antagonist, can control the activity of the receptor by binding to the receptor. For the combination therapy, including memantine and donepezil, has a significant improvement on cognitive judgment, language, and behavior of moderate to severer AD patients. Unfortunately, because of the complexity of AD pathogenesis, these drugs only temporarily relieve the symptoms of AD. There are currently no therapies available to prevent, treat, or reverse the course of AD. Thus, researchers began to find out other drugs that can fundamentally treat AD [10].

More and more ongoing clinical trials are carried out. Depending on the pathogenesis of AD, prevailingly focusing on Abeta and tau protein, there are two kinds of therapeutics: drugs targeting Abeta production, Abeta or formation of amyloid aggregation, and drugs targeting tau protein deposition and hyperphosphorylation. In order to restrain the overproduction of Abeta, alpha-secretases stimulators (e.g. epigallocatechin-gallate, EGCG, Sunphenone), beta-secretases inhibitors (e.g., Lanabecestat and Umibecestat), and gamma-secretases inhibitors (e.g., Semagacestat) can all theoretically retard the process of Abeta production, relieving the symptoms of AD. Tarenflurbil, an example of therapy targeting Abeta directly, reduces the content of Abeta 42, and Tramiprosate, an example of drug targeting formation of amyloid aggregation, inhibits the aggregation and hence, prevents the formation of beta-sheet. Aiming to block the deposition and hyperphosphorylation of tau protein, Blarcamesine (ANAVEX2-73) focuses on protein misfolding and reduces tau hyperphosphorylation, oxidative stress, and neurodegeneration in AD, being a muscarinic receptor agonist and a sigma-1 receptor activator. Besides, many other various therapies, such as drugs targeting neuroinflammation (ALZT-OP1) and miscellaneous targets (Azeliragon, TTP488) can also treat AD

theoretically in different ways. Vaccines are also under progress, such as AADvac1 [10]. Nevertheless, more than 50 drugs successfully progressed from phase 2 (evaluation of the efficiency and safety of new drugs) to phase 3 (the effectiveness of the drug used in several thousands of patients), but only one agent passed the phase 3 clinical trial since 2003 - Aducanumab.

However, neither non-drug therapy nor drug therapy can fundamentally treat AD, but only relieve AD from symptoms. The side effects of drugs cannot be ignored, such as extrapyramidal symptoms and the burden of drug metabolism on the liver and kidneys in the body. Moreover, the progress of cognitive impairment in AD patients also leads to a decrease in compliance of treatment, so that the related intervention methods cannot achieve the expected goals. The economic burden brought by precision medicine is also a factor that must be considered, whether AD patients can afford the high treatment costs. In the future, it is still necessary to further open up new treatment options in order to better help improve the quality of life of AD patients.

4. The Aducanumab for AD

Aducanumab is an IgG1 monoclonal antibody, acting as the drug targeting Abeta. Its mechanism of action is to selectively target low aggregates and insoluble fibrin fibril conformations that bind to soluble beta plaques aggregated within the brain by crossing the blood-brain barrier. This can extend its conformation to the n-terminal of Abeta, making it more selective to Abeta that gathers. Therefore, Abeta plaques of the brain are reduced [11].

What is worth mentioning is that Aducanumab has made great progress in studying animal models of AD. In the 2021's AD mice experiment from Bastrup Joakim et al., chronic treatment with aducanumab has been proven to have the ability to inhibit Abeta toxicity and increasing phagocytosis and cell viability. By chronic treatment with weekly administration of aducanumab (10mg/kg) for four months, laser fiber dissection and LC-MS/MS were used to analyze the remaining SP in the hippocampus. In aducanumab-treated mice, 17 significantly regulated proteins were detected. The first was mitochondrial and metabolism-related proteins, such as ETFA, EXOG, NDUFS7, PPP2R4, and others. The second is proteins associated with cytoskeleton establishment and axogenesis stabilization, such as ADD1, DPYSL3, and MAG. The third is the common and stress-related proteins, the most classic HIST1H1 and HSPA12A and so on. The last one is a typical functional protein related to Abeta/APP transport/processing, especially CD81 and GDI2. In previous studies, the relationship of these proteins to the pathogenesis of AD has been elucidated. Some are also briefly described above. Furthermore, the first proteins are mainly up-regulated and the fourth proteins are mainly down-regulated. This is a good indication that aducanumab leads to a beneficial proteomic analysis [12]. In another experiment in mice taken by Chanho Kong et al. in 2022, they discovered that low-dose aducanumab through focused ultrasound (FUS) enhanced delivery reduces amyloid precipitation and restores cognitive function. FUS combined with aducanumab was treated a total of three times on mice. Through gene expression profile of the hippocampus measured, the result found that FUS treatment increases the amount of ADU entering the brain by about 8.1 times. This combination treatment can increase the reactive microglia and amyloid plaque associated with the hippocampus in 5xFAD mice, thereby lowering the formation of amyloid plaques in the hippocampus and restoring cognitive dysfunction in mice [13].

Although aducanumab is the only drug approved by FDA to treat AD, there is a considerable controversy among people. The primary evidence for the efficacy of aducanumab is two nearly identically designed placebo-controlled randomized phase 3 clinical trials. CDR-SB was used in these two studies, which is a composite measurement that contains cognitive and functional components, such as problem solving [14]. Interestingly, these two identically designed experiments had very different even conflicting results. The 301 study (1647 randomized patients) did not achieve the principal reduction relative to placebo in the CDR-SB scores. Based on pre-formulated protocols to prevent erroneous conclusions from multiple analyses, no secondary endpoint of the 301 study can be a statistically valid conclusion. In contrast, study 302 (1638 randomized patients) achieved statistically

significant treatment outcomes at its primary endpoint, estimating high-dose efficacy compared to placebo. The results corresponded to a 22% relative decrease in CDR-SB outcomes. In the low-dose aducanumab group of the 302 study, the effect was not compared to placebo. It was statistically significant and based on a pre-specified analytical plan, which excluded the ability to assess secondary outcomes of efficacy in both high- and low-dose groups [14]. Therefore, this seems to be less persuasive and objective to prove that aducanumab can be used for AD treatment in only by a single trial. Additionally, there are also two other concerns about the promotion of aducanumab: the side effect and the price of the medication. In clinical trials, aducanumab has been associated with amyloid-associated imaging abnormalities (ARIA)-cerebral edema (ARIA-e) or new microbleeds/jaundice (ARIAh). Most of these abnormalities are asymptomatic. Only 24 percent of patients develop treatment-related symptomatic ARIA, most of whom resolve spontaneously. Occasionally, severe symptoms occur in patients. Although routine MRI screening is used for asymptomatic ARIA and guidance on how to handle symptomatic cases, but aduzumab is adux-for-life scenarios, the condition of aducanumab remains to be determined. It is unclear whether this affects the risk or efficacy [15]. Speaking to the cost, aducanumab will be sold at the price of $56 000 per person each year [2,15]. This vast cost will increase the stress on families of AD patients. Also, the uncertainty about the efficiency of the aducanumab and the length of the treatment may bring their family's false hope.

5. Conclusion

Howbeit, aducanumab is the only new drug for AD approved by FDA up to now; it can reduce Abeta plaque in the brain by targeting low aggregates and insoluble fibrinofibril conformations. Due to the conflicting results of two identically designed studies (study 301 and 302), the efficiency of aducanumab still has a question. Usually, there are two main concerns about the promotion of this new drug: side effects and the high cost. Although the harm of side effects-ARIA is negligible in most situations, there is also unclear whether this affects the risk. The ordinary people cannot afford the such a high cost of the drug, making it impossible to continue treatment. In the future, another primary cause of AD may be found out to extend the view of AD. New drugs should be created and promoted. The drugs targeting tau protein may be the next topic for therapeutics. The field of AD has a long way to go.

References

[1] T. Zhao et al, (2019) Identifying Alzheimer's disease-related proteins by LRRGD. BMC Bioinform., 20 (18): 1-9. J. Clerk Maxwell, A Treatise on Electricity and Magnetism, 3rd ed., vol. 2. Oxford: Clarendon, 1892, pp.68 – 73.

[2] S. Walsh et al, (2021) Aducanumab for Alzheimer's disease? BMJ., 374.

[3] A. Kowalska, (2004) The beta-amyloid cascade hypothesis: a sequence of events leading to neurodegeneration in Alzheimer's disease. Neurol. Neurochir. Pol., 38 (5): 405 - 411.

[4] S. Muralidar et al, (2020) Role of tau protein in Alzheimer's disease: The prime pathological player. Int. J. Biol. Macromol., 163: 1599 - 1617.

[5] S. Ohta and I Ohsawa, (2006) Dysfunction of mitochondria and oxidative stress in the pathogenesis of Alzheimer's disease: on defects in the cytochrome c oxidase complex and aldehyde detoxification. J. Alzheimer's Dis., 9 (2): 155 - 166.

[6] H. Hampel et al, (2019) Revisiting the cholinergic hypothesis in Alzheimer's disease: emerging evidence from translational and clinical research. J. Prev. Alzheimer's Dis., 6 (1): 2 - 15.

[7] J. Olazarán et al, (2010) Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dement Geriatr Cogn Disord., 30 (2): 161 - 178.

[8] C. Zucchella et al, (2018) The Multidisciplinary Approach to Alzheimer's Disease and Dementia. A Narrative Review of Non-Pharmacological Treatment. Front Neurol., 9: 1058.

[9] Y. Shigihara et al, (2020) non-pharmacological treatment changes brain activity in patients with dementia. Sci Rep., 10 (1): 1 - 9.

[10] T. Athar et al, (2021) Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease. Mol. Biol. Rep., 48 (7): 5629 - 5645.

[11] A. Zainab, (2022) The mechanism of action of the controversial drug; aducanumab and the story behind its speedy approval. J Pak Med Assoc., 72 (5): 1019.

[12] J. Bastrup et al, (2021) Anti-Aβ antibody aducanumab regulates the proteome of senile plaques and closely surrounding tissue in a transgenic mouse model of Alzheimer's disease. J. Alzheimer's Dis., 79 (1): 249 - 265.

[13] C. Kong et al, (2022) Enhanced delivery of low-dose of aducanumab via FUS in 5xFAD mice, an AD model. http://www.researchsquare.com/article/rs-1891775/v1.

[14] G. C. Alexander et al, (2021) Evaluation of aducanumab for Alzheimer disease: scientific evidence and regulatory review involving efficacy, safety, and futility. Jama., 325 (17): 1717 - 1718.

[15] J. Cummings et al, (2021) Aducanumab produced a clinically meaningful benefit in association with amyloid lowering. Alzheimer's Res. Ther., 13 (1): 1 - 3.

[16] G. Lalli et al, (2021) Aducanumab: a new phase in therapeutic development for Alzheimer's disease. EMBO Mol. Med., 13 (8): e14781.