(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 4, Issue 4, Page No: 234-239
July-August 2021

IJMSCR

BDNF Gene Therapy as An Alzheimer's Disease Treatment

Chollaphin Wilairatanarporn*, Monrada Chiewhawan, Pimnapa Ruangkam
Triam Udom Suksa School

***Corresponding Author:**
Chollaphin Wilairatanarporn
Triam Udom Suksa School

Type of Publication: Case Report
Conflicts of Interest: Nil

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease affecting millions of lives. The prevalence of AD continues to rise without effective treatment. Though aging is one of the key factors, the understanding of its etiology is still limited. Most of the current treatments are treating the symptoms rather than the underlying course of the disease. The disease-modifying drug is also based mainly on the controversial amyloid hypothesis. Therefore, we aim to investigate other existing approaches, the BDNF gene therapy in particular. In this paper, we will discuss what BDNF gene therapy is, as well as its advantages and disadvantages. Through the process of reviewing studies and information from 2005 to 2021, we have learned that human clinical trials are still underway, and more research should be done before proclaiming BDNF gene therapy as an effective AD treatment.

Keywords: Alzheimer's Disease, BDNF Gene Therapy, Treatment

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia, a usual term for memory defects and other cognitive impairments that seriously affect daily life. This disease can be described as a progressive neurodegenerative disease that exhibits characteristic cellular and molecular pathologies in the brain, including the accumulation of amyloid-β (Aβ) and formation of tau neurofibrillary tangles inside neurons. According to the Alzheimer's Association annual report 2020, more than 6 million Americans are living with AD. By 2050, this number is projected to rise to nearly 13 million. The latest year record showed that AD was the sixth-leading cause of death in the United States. This increase in deaths was likely exacerbated during the Covid-19 pandemic. AD causes the brain to shrink and neurons to die especially in the hippocampus which plays a critical role in forming and storing new memories. However, it remains unclear how cellular and molecular disturbances in AD affect coordinated activity across the networks of neurons that subserve memory operations. The well-known threatening factor is aging, and most people with AD are 65 years old and older—late-onset AD (95–97% prevalence). Nonetheless, AD is not considered as a typical part of normal aging. This degenerative disease can also affect people with ages ranging from 40 to 65 years old which is called early-onset AD (3–5% prevalence). Accordingly, early cognitive symptoms of AD involve episodic and spatial memory impairments. As the disease progresses, a person with AD will lose the ability to carry out everyday tasks—thinking and reasoning, making judgments and decisions, performing familiar tasks. Moreover, they can change in personality and behavior. Doctors use several methods and tools to identify AD patients, e.g., asking the person and family members about overall health, conducting tests of cognitive functions, performing brain scans. It is important to note that AD can be definitively diagnosed only after death, by linking clinical measures with an examination of brain tissue in an autopsy. This disease is still incurable, but current

treatment strategies can momentarily reduce the deterioration of the symptoms and progress the quality of the patient's life.

Currently, there are various treatments for AD according to different hypotheses aimed at explaining the origins of AD—Cholinergic hypothesis, Amyloid hypothesis, tau hypothesis, and others. Several prescription drugs are approved by the U.S. Food and Drug Administration (FDA) to treat the symptoms. Most medicines work best for people in the early or middle stages of AD, divided into three classes: Cholinesterase inhibitors; NMDA receptor antagonists; and targeting amyloid-β plaques. These drugs may help reduce some symptoms and help control some behavioral symptoms but they cannot cure the disease or stop its progression. However, new experimental drugs are now being developed to target underlying causes. One of the major promising targets for future drugs is preventing amyloid-β fragments from clumping into plaques by targeting two enzymes, β-secretase, and γ-secretase. Furthermore, scientists are now finding alternative ways to treat this disease by applying medical technology to medication for AD patients, e.g., stem cell, brain wave stimulation, immunotherapy, vaccine, nanotechnology, and brain-derived neurotrophic factor (BDNF) gene therapy. In this paper, we will discuss the efficacy and limitations of using BDNF gene therapy which appears to have the potential to become a disease-modifying treatment for AD.

The Current Treatment

In general, there is yet a sole treatment that could cure Alzheimer's disease as it is a progressive neurodegenerative disease that typically develops a couple of years before a diagnosis, and its underlying cause is still a controversial subject. Moreover, effective AD management requires a holistic approach from an early diagnosis to a customized care plan to nonpharmacologic and pharmacologic approaches [6]. Nonetheless, this section is to discuss pharmacology for AD patients in the present.

Most medications prescribed to AD patients currently are those that deal with the disease symptomatically. As of June 2021, only three categories are approved by the FDA to deal with cognitive symptoms of AD: cholinesterase inhibitors (ChE-Is); N-methyl-D-aspartate (NMDA) receptor antagonists; and the combination of the previous ones. Firstly, cholinesterase inhibitors are a group of medications that prevent the breakdown of the neurotransmitter acetylcholine, supporting communication between neurons. They are usually prescribed to treat symptoms related to thinking, judgment, memory, etc. Donepezil, rivastigmine, and galantamine are the approved ChE-Is. Secondly, N-methyl-D-aspartate (NMDA) receptor antagonists are a type of glutamate regulator prescribed to improve memory, attention, reason, etc. They inhibit NMDA receptors which have shown to be related to synaptic dysfunction and ultimate neural death. The only approved NMDA receptor antagonist is memantine. The last category, the combination of ChE-I and NMDA regulator, has only one category approved, a mixture of donepezil and memantine. It is used for moderate-to-severe AD.

For non-cognitive symptoms, the orexin receptor antagonist for treating insomnia is the only category approved for patients living with dementia. It is thought to inhibit orexin, a neurotransmitter related to the sleep-wake cycle. Suvorexant is the only one accepted so far.

Another type of medication is disease-modifying drugs. They target the underlying course of AD. Many notable ones attempted to reduce the Aß plaque. The amyloid theory suggested that Aß accumulation can result in excitotoxicity and play important roles in the pathogenic cascade. Aß peptide, which is the main component of the Aß plaque, is formed when the amyloid precursor protein (APP) is cleaved by β- and γ-secretase. Therefore, these medications tend to inhibit either β- or γ-secretase. Though they can reduce Aß plaque, these medications failed to show clinical benefits. As a result, there were mixed opinions of whether the failure was due to the insufficient amount of dosage or the limited understanding of the disease etiology.

Interestingly, a new medication, Biogen's aducanumab, was approved under the accelerated approval pathway by the FDA on June 7 after no drug treating AD had been approved since 2003. Originally, its phase III studies—which were EMERGE and ENGAGE—were halted in March 2019 due to divergent results. After a subsequent analysis, Biogen announced that both studies actually suggested efficacy signals and submitted a New Drug Application to the FDA in 2020. Its approval without apparent proof of efficacy and its involvement with the

Volume 4, Issue 4; July-August 2021; Page No 234-239

amyloid hypothesis generated a debate on whether the FDA made the right decision or not. Since it is the first and only distributable disease-modifying drug for AD, such uncertainties could result in various difficulties. Though a post-approval trial is required to prove its surrogate endpoint which is the removal of Aβ plaque, damages might be done before its efficacy is finalized.

Therapeutic approaches have the advantage of being less costly and requiring less complicated processes during clinical trials. However, the understanding of the pathophysiology of AD is still limited, causing the efficacy of this method to be questionable.

What is BDNF Gene Therapy?

Unlike most existing treatments of AD, brain-derived neurotrophic factor (BDNF) gene therapy, along with other underdeveloped techniques, aims to be a treatment for the underlying cause of AD.

Gene therapy is a medical treatment involving genetic alteration, which has been studied over a decade in an attempt to be curative of patients with AD [17], as its concept has been successfully utilized to cure other severely progressive diseases, such as cancer. Primarily, as an approach to treat AD symptoms, this therapeutic treatment is used to modify protein in the neurotrophin family including brain-derived neurotrophic factor (BDNF). BDNF is the key regulator of synaptic plasticity. Normally, it is continually produced throughout life in the entorhinal cortex and hippocampus, the essential proportion in the brain that supports memory. However, it evidently degenerates in people diagnosed with AD. As a result of the suspected connection between BDNF and the presence of AD, BDNF gene therapy has been developed and tested over time. Significantly, in wake of success in reversing the loss of connections and, preventing the degeneration of cells in animal models, including aged rats, aged monkeys and amyloid mice, the treatment has recently been launched to be assessed in Phase I clinical trial in which 12 participants, either diagnosed with AD or mild cognitive impairment (MCI), will receive an injection of BDNF gene carried by a harmless adeno-associated virus (AAV2), and another 12 people will serve as an untreated control group [18]. Furthermore, the trials using BDNF achieved improvements over the ones using Nerve Growth Factor (NGF), a protein belonging to the neurotrophin family that was tested but eventually failed to be delivered to the brain.

In consideration of the precision of targeting the entorhinal cortex, the procedure involves inserting an MRI-compatible needle into the region of the brain that is primarily affected by AD. Subsequently, the delivery of AAV2, an engineered carrier virus, into the nerve cells is performed. In order to track the distance of the dispersion from the injection site, an MRI contrast agent is also infused. Eventually, it is expected that the transportation of BDNF in AAV2 reaches the hippocampus and does not enter any healthy neurons; otherwise, seizures or other side effects can be caused.

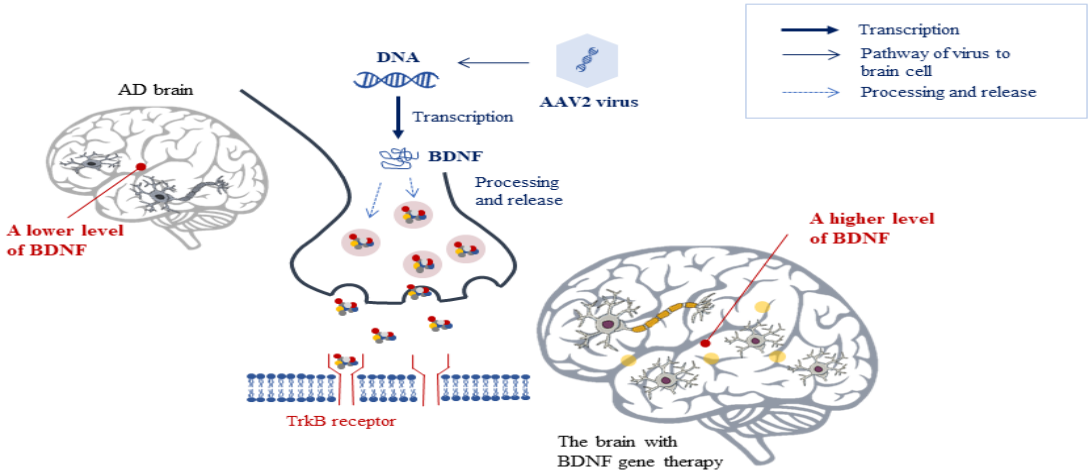

Figure 1: Mechanism of BDNF Gene Therapy

Volume 4, Issue 4; July-August 2021; Page No 234-239

Case For BDNF Gene Therapy in treating AD

As opposed to NGF administration, BDNF is proclaimed to be more beneficial, thereby being a more promising curative treatment of AD. Significantly, BDNF acts directly on degenerating cells in the cortical region, a specific memory circuit of the brain. Furthermore, the restorative and protective impacts of the protein are prompted independently of the accumulation of amyloid. Additionally, performing gene therapy will allow BDNF to be regenerative again just like in normal people. Therefore, the potential of BDNF is relatively greater than other administrations.

Case Against BDNF Gene Therapy in treating AD

In regards to a causal link between the generation of BDNF and the progression of neurodegeneration due to the occurrence of AD, there are some inconsistencies in studies of interest. BDNF is found to increase in patients diagnosed with MCI, which in AD, on the other hand, is found to decrease. Therefore, it is recommended that researchers and scientists conduct trials with the acknowledgment of this crucial piece of information. Moreover, to date, it is still a big challenge for the protein molecule to get through the blood-brain barrier (BBB), in spite of advanced technologies in use. As aforementioned, the previous attempt to deliver NGF was also a failure. The process requires precise delivery of the protein to the targeted regions of the brain as detrimental effects can be expected if BDNF freely circulates. In addition to the precise delivery, the appropriate amount of protein expression is also another challenge of concern. However, it might be more hopeful of acquiring an effective delivery and distribution method, regarding the rapid development of technology.

CONCLUSION

The trend of Alzheimer's disease is rising while there is still little knowledge and cure for it. The current therapy is medication. However, most of them are still those that only treat the symptoms rather than altering its underlying course. Though the approval of aducanumab excited many because of its potential and the FDA's absence of approval for over a decade, it still raised multiple concerns and controversies. It certainly is crucial to investigate more in this matter since it involves millions of lives. This could also be the time to test the amyloid theory and pave a way for the future of Alzheimer's disease treatments. Other than drugs, many methods have shown to be promising. As discussed here in this paper, the brain-derived neurotrophic factor gene therapy is one of them. This treatment directly targets the degenerative cells, not the amyloid plaque. As BDNF plays an important role in memory and shows relation with AD, BDNF gene therapy represents a curative potential. The therapy involves injecting a harmless virus carrying BDNF gene. It is expected to increase synaptic connections between neurons. The trials on animal models were successful. However, human clinical trials are still in Phase I. Thus, it is still premature to conclude its efficacy. Furthermore, the BDNF molecule delivery process is complicated because of the blood-brain barrier. Many attempts are underway to tackle this challenge and improve the technique. As the etiology of AD is yet fully understood, research and trials are the main keys to drive AD treatments closer to success.

REFERENCE

1. Atri. (2019, March). The Alzheimer's Disease Clinical Spectrum: Diagnosis and Management. ScienceDirect. https://doi.org/10.1016/j.mcna.2018.10.009
2. Medications for Memory, Cognition and Dementia-Related Behaviors. (n.d.). Alzheimer's Association. Retrieved June 11, 2021, from https://www.alz.org/alzheimers-dementia/treatments/medications-for-memory
3. FDA-approved treatments for Alzheimer's. (2021). Alzheimer's Association. https://www.alz.org/media/documents/fda-approved-treatments-alzheimers-ts.pdf
4. Cummings, J. (2021, April 1). New approaches to symptomatic treatments for Alzheimer's disease. Molecular Neurodegeneration. https://molecularneurodegeneration.biomedcentral.com/articles/10.1186/s13024-021-00424-9
5. Acetylcholinesterase Inhibitors: Pharmacology and Toxicology. (2013, May 1). PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3648782/

Volume 4, Issue 4; July-August 2021; Page No 234-239

6. The Role of NMDA Receptors in Alzheimer's Disease. (2019). PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6375899/
7. Office of the Commissioner. (2021, June 7). FDA Grants Accelerated Approval for Alzheimer's Drug. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug
8. SAGE Journals: Your gateway to world-class research journals. (2020, February 29). SAGE Journals. https://journals.sagepub.com/doi/full/10.1177/1179573520907397
9. Center for Drug Evaluation and Research. (2021, June 22). Aducanumab (marketed as Aduhelm) Information. U.S. Food and Drug Administration. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/aducanumab-marketed-aduhelm-information
10. Lowe, D. (2021, June 8). The Aducanumab Approval | In the Pipeline. In the Pipeline | Derek Lowe's Commentary on Drug Discovery and the Pharma Industry. An Editorially Independent Blog from the Publishers of Science Translational Medicine. https://blogs.sciencemag.org/pipeline/archives/2021/06/08/the-aducanumab-approval
11. Knopman, D. S. (2021, April 1). Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimer's Association. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.12213
12. Center for Biologics Evaluation and Research. (2018, July 25). *What is Gene Therapy?* U.S. Food and Drug Administration. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy
13. Scheller, E., & Krebsbach, P. (2009, July 01). Gene Therapy: Design and Prospects for Craniofacial Regeneration. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907101/
14. Fliesler, N. (2020, December 22). *A short history of gene therapy - Boston Children's Discoveries*. Boston Children's Answers. https://answers.childrenshospital.org/gene-therapy-history/
15. Mandal, A., MD. (2019, February 27). *Gene Therapy History*. News-Medical.Net. https://www.news-medical.net/health/Gene-Therapy-History.aspx
16. *Gene therapy - Mayo Clinic*. (n.d.). Https://Www.Mayoclinic.Org/Tests-Procedures/Gene-Therapy/about/Pac-20384619. Retrieved June 28, 2021, from https://www.mayoclinic.org/tests-procedures/gene-therapy/about/pac-20384619
17. LaFee, S. (2021, February 18). *First-in-Human Clinical Trial to Assess Gene Therapy for Alzheimer's Disease*. UC Health - UC San Diego. https://health.ucsd.edu/news/releases/Pages/2021-02-18-first-in-human-clinical-trial-to-assess-gene-therapy-for-alzheimers-disease.aspx
18. F. (2021, March 1). *Phase 1 Trial to Test BDNF Gene Therapy in Alzheimer's Patients*. Alzheimer's News Today. https://alzheimersnewstoday.com/2021/03/01/phase-1-trial-university-california-san-diego-ucsd-bdnf-gene-therapy-aav2/
19. Seydel, C. (2021, March 12). *Clinical Trial Begins For Gene Therapy To Treat Alzheimer's Disease*. Forbes. https://www.forbes.com/sites/carolineseydel/2021/03/12/clinical-trial-begins-for-gene-therapy-to-treat-alzheimers-disease/?sh=6b3827227171
20. Giacobbo, B. L. (2018, August 17). *Brain-Derived Neurotrophic Factor in Brain Disorders: Focus on Neuroinflammation*. Molecular Neurobiology. https://link.springer.com/article/10.1007/s12035-018-1283-

Volume 4, Issue 4; July-August 2021; Page No 234-239

6?error=cookies_not_supported&code=a64b51f9-0bab-4747-86b8-3de61eb82d35

21. Fumagalli, F. (2005, November 29). *The expanding role of BDNF: a therapeutic target for Alzheimer's disease?* The Pharmacogenomics Journal. https://www.nature.com/articles/6500337?error=cookies_not_supported&code=b6895ef2-9e7b-4844-98b6-9c721541a09d
22. *Growth Factor Protects Key Brain Cells in Alzheimer's Models*. (n.d.). Https://Ucsdnews.Ucsd.Edu/Archive/Thisweek/2009/02/16_GrowthFactorAlzheimers.Asp. Retrieved June 28, 2021, from https://ucsdnews.ucsd.edu/archive/thisweek/2009/02/16_GrowthFactorAlzheimers.asp
23. Kennington, E. (n.d.). *Gene therapy delivers an alternative approach to Alzheimer's disease*. Nature Reviews Drug Discovery. Retrieved June 28, 2021, from https://www.nature.com/articles/nrd2855?error=cookies_not_supported&code=da8add5a-c520-4e89-9717-3508f203b96e
24. Wu, C. (2016, June 6). *Gain of BDNF Function in Engrafted Neural Stem Cells Promotes the Therapeutic Potential for Alzheimerâs Disease*. Scientific Reports. https://www.nature.com/articles/srep27358?error=cookies_not_supported&code=57f5e631-83d1-4d7b-83b4-b978049270fb
25. *How Is Alzheimer's Disease Treated?* (n.d.). National Institute on Aging. Retrieved June 28, 2021, from https://www.nia.nih.gov/health/how-alzheimers-disease-treated
26. *Alzheimer's treatments: What's on the horizon?* (2021, May 20). Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers-treatments/art-20047780
27. *How Important Is the Hippocampus in the Brain?* (n.d.). Verywell Mind. Retrieved June 28, 2021, from https://www.verywellmind.com/what-is-the-hippocampus-2795231
28. *Alzheimer's disease - Symptoms and causes*. (2021, June 26). Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/symptoms-causes/syc-20350447
29. Uddin, M. S. (2018, November 29). Introductory Chapter: Alzheimerâs DiseaseâThe Most Common Cause of Dementia. IntechOpen. https://www.intechopen.com/books/advances-in-dementia-research/introductory-chapter-alzheimer-s-disease-the-most-common-cause-of-dementia
30. Folch, J. (2016, January 3). Current Research Therapeutic Strategies for Alzheimer's Disease Treatment. Jaume Folch. https://www.hindawi.com/journals/np/2016/8501693/
31. Facts and Figures. (n.d.). Alzheimer's Disease and Dementia. Retrieved June 28, 2021, from https://www.alz.org/alzheimers-dementia/facts-figures
32. *What is Alzheimer's Disease | CDC*. (n.d.). Https://Www.Cdc.Gov/Aging/Aginginfo/Alzheimers.Htm. Retrieved June 28, 2021, from https://www.cdc.gov/aging/aginginfo/alzheimers.htm
33. Page not available. (n.d.). Ncbi. Retrieved June 28, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5762114/

Volume 4, Issue 4; July-August 2021; Page No 234-239