Optimizing Drug Efficacy in Late-Onset Alzheimer's Disease Through Combination Treatment

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Introduction to Alzheimer's Disease (AD)

In our current world, 6.7 million Americans above the age of 65 are living with Alzheimer's Disease (AD). If no treatment is found, by 2060, this number could go to 13.8 million ("2023 Alzheimer's…"). While there are multiple theories for the causation of AD, including a sustained immune response, inflammation, and glucose metabolism derangement, this paper will focus on the amyloid hypothesis (Huang). The amyloid hypothesis states that amyloid accumulation is the major biological event leading to AD, followed by neuroinflammation, neurofibrillary tangles, and eventual cell death (Cummings). Furthermore, the disease is correlated with abnormal buildup of amyloid-beta and tau ("What Causes Alzheimer's Disease?"). These amyloid-beta plaques misfold and disrupt cell function by injuring the neurons and their connections with other neurons. These buildups increase the toxicity in the central nervous system (CNS), leading to necrosis of neurons in the brain. Necrosis of neurons can lead to the atrophy of the brain because many regions in the brain begin to shrink from the loss ("What Happens to the Brain …"). This neurodegenerative disease varies in severity, from mild AD to severe AD, but all types of Alzheimer's involve memory loss, inability to do daily tasks, repeating questions, loss of direction and initiative, and other forms of escalating deterioration of brain function (Huang).

Clinicians have many methods to identify a patient's stage of Alzheimer's disease. One method is through cognitive screening and assessment. People can apply for cognitive screening if they or their relatives notice symptoms, including but not limited to personality changes or chronic depression. One test is called the General Practitioner Assessment of Cognition. This test is a "screening tool for cognitive impairment designed for use in primary care and is available in multiple languages" ("Cognitive Screening and Assessment"). Another test is the Mini-Cog, which is a three-minute exam based on a recall test of memory and a clock-drawing test. There are also various digital cognitive testing tools, such as ANAM and Cognigram ("Cognitive Screening and Assessment"). Finally, another tool for cognitive testing is the amyloid PET scan. This scanning tool visualizes amyloid plaques present in the brain that have been shown to be correlated with the advancement of the disease. When the scan occurs, the plaques appear on the screen, leading to their accurate detection ("Amyloid PET Scan …").

Furthermore, there are two types of AD, early-onset AD (EOAD) and late-onset AD (LOAD). Early onset affects patients between 30 and 60 years old and is very rare. Heritable risk is a large contributor to EOAD. Late-onset AD affects patients in their mid-60s or older and is the most common type of AD. A driving factor for LOAD is two alleles of apolipoprotein E (APOE) ε4. The apolipoprotein E gene is involved in making a protein that carries cholesterol and other lipids down the bloodstream, and issues in this process are connected to the continuation of AD ("Alzheimer's Disease Genetics …"). In the brain, APOE has a specific role. According to "Neuroimaging: Technologies at the Interface of Genes, Brain, and Behavior", APOE is needed for functions such as "neuronal growth and repair, neuroprotection, and inflammation" (Bigos). There are three alleles of APOE: APOE ε2, APOE ε3, and APOE ε4. APOE ε2 is the rarest allele of APOE, and it decreases the risk of AD. APOE ε3 is the most common allele, and it is shown to have a neutral effect on AD. Finally, there is APOE ε4, which

is linked to having an increased risk for AD, and a worse type of AD ("Alzheimer's genes…"). APOE ε4 is a serious risk factor for LOAD because having just one allele increases the risk of AD two or threefold, but having two alleles increases your risk by eight to twelvefold. Interestingly enough, many people with both alleles do not get AD, and others with APOE ε2 still get the disease. This means that APOE alleles only influence the outcome of AD in a patient, and are not an inherent cause ("Alzheimer's genes…"). An important thing to consider is that APOE ε4 is not always bad. It is suggested that possessing the APOE ε4 allele is advantageous earlier in life but leads to a faster decline of cognitive function later (Zokaei). My paper focuses on LOAD because it is more common, consequently affecting a wider demographic of patients. Currently, in the world of Alzheimer's disease, the lack of effective therapeutics is felt by all AD patients, and researchers haven't found a cure yet for this neurodegenerative disease.

Lecanemab Therapy

Lecanemab is a monoclonal antibody that is used in the treatment of AD. According to the Cleveland Clinic, antibodies are proteins that protect you when unwanted substances and antigens enter your body. These antibodies attack and fight off the foreign antigens ("Antibodies…"). Monoclonal antibodies are a type of antibody, with the main difference being that monoclonal ones are produced in a laboratory, cloned from an actual antibody with one specific target. These monoclonal antibodies mimic the way that regular antibodies function in the immune system to fight off antigens, and this is a common form of immunotherapy ("Antibodies…"). Antibodies, made by your immune system or in a lab, work uniquely with phagocytes. Phagocytes are immune cells that surround and absorb pathogens in the body, and when a monoclonal antibody attaches itself to a pathogen, phagocytes surround the complex and proceed to absorb and destroy the pathogen (Newman).

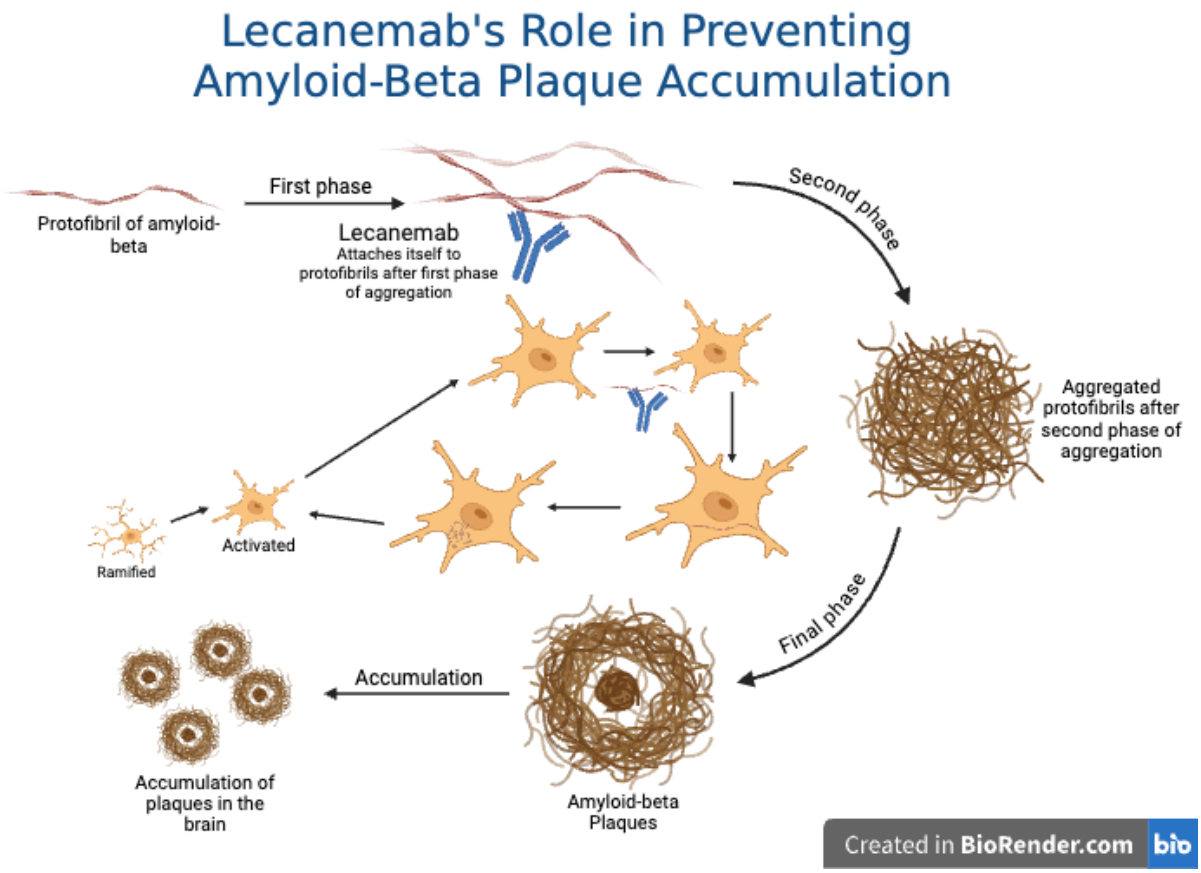

Figure 1: This figure shows the different stages of amyloid-beta plaque accumulation. Lecanemab is shown to bind to protofibrils after the first phase of aggregation. Afterward, activated microglia interact with the lecanemab and proceed to consume and destroy the amyloid-beta, averting plaque accumulation. (Created with BioRender.com).

Lecanemab was released on July 6, 2023, by Leqembi, after being approved by the FDA. It is administered via IV infusion and targets amyloid-beta plaques as its antigen ("Lecanemab Approved …"). This specific type of antibody targets the amyloid-beta by binding to protofibrils after the first phase of aggregation (Fig. 1). Protofibrils aggregate and form these buildups of amyloid-beta (Abbott). Lecanemab binds to these protofibrils and moves them away from each other to bar them from combining. Microglial cells then absorb and destroy the amyloid-beta in its activated state (Fig. 1)(Butovsky and Weiner).

In a large clinical study by Eisai, Lecanemab slowed AD progression by 20 to 30 percent after 18 months of therapy (Van Dyck). Only AD patients in the early stages of AD and with some amount of accumulation of amyloid in the brain should take Lecanemab. Furthermore, patients with other forms of dementia unrelated to the buildup of amyloid beta should not take this drug. Finally, patients with a gene type APOE ε4 should be cautious before taking Lecanemab, as it has been shown that patients with this gene type experience more severe side effects("Lecanemab"). Other monoclonal antibodies that treat Alzheimer's disease target protofibrils at earlier or later stages of aggregation (Abbott). Lecanemab is a great step forward in the world of medication for Alzheimer's, but it still has its side effects. Some of them include

headaches and possible allergic reactions ("Lecanemab Approved …"). Furthermore, Lecanemab is just a treatment for the disease, not a cure. Lecanemab will not reverse symptoms, such as returning lost memories or restoring previous cognitive function. It will only plateau the situation of a patient with mild to moderate Alzheimer's disease ("Lecanemab Approved …"). The search for a drug that cures AD is a long and frustrating journey for many scientists and researchers.

Introduction to Focused Ultrasound (FUS)

Focused ultrasound (FUS) is being tested in multiple clinical trials today for the treatment of AD, and by itself has been known to reduce some symptoms of AD, like memory reduction, amyloid, and tau (Noel). Focused ultrasound is a procedure that uses concentrated sound waves to treat different conditions. In this type of treatment, sound waves are concentrated through an acoustic lens, which directs these concentrated waves to a specific point on the body ("Focused Ultrasound"). After passing through the acoustic lens, the sound waves heat up and either destroy or change patches of affected tissue without influencing surrounding tissue. FUS is a non-invasive procedure, meaning that no instruments are required to be inserted into the body ("Focused Ultrasound"). The state of FUS being non-invasive provides sundry benefits: it can reach deep targets inside the body, boasts high precision by having a target radius of 1 by 1.5 mm, and allows for quick recovery time as no full anesthesia and surgery is required ("Focused Ultrasound").

The effectiveness and the duration of FUS on AD are elusive. Still, the results of one trial show that low-frequency stimulation to the back of the brain can help with short-term memory, and high-frequency stimulation to the front of the brain can help with long-term memory (Contie). Some trials have found that in combination with drug therapy can boost positive results in patients. Drug therapies are usually ineffective because they are rejected by the brain and cannot cross the BBB. The BBB is used to describe the unique properties of the barrier between the CNS blood vessels and the CNS itself (Daneman). The CNS blood vessels are nonfenestrated, meaning they have no pores or openings, but they have additional attributes that allow for restricted regulation of ions and molecules between the barrier. This tight regulation of CNS homeostasis permits optimal neuronal function and protects the brain from unwanted pathogens and disease (Daneman). This also includes drug therapies intended to support the neurons and clear amyloid. Due to the tight regulation, only a minimal amount of the drug enters the brain and performs its specified task, leading to large doses of the drug needed, which causes many unwanted side effects (Daneman).

FUS, on the other hand, could help with this predicament. The first step in a FUS treatment is to precisely inject microbubbles into the blood vessels (Lin). The FUS would then have to be positioned towards the hippocampus, where amyloid pathology is a consistent feature of AD or any other area with significant pathology (Dhikav). When the ultrasound is turned on, it hits blood vessels in the hippocampus, and the bubbles being hit by the sound waves begin to pulse, expanding and retracting as it passes through them (Lin). This would cause the otherwise strong and tight sections between blood vessels and the brain to open up

slightly. This breach of the blood-brain barrier would allow the specified drug therapy to seep into the brain and help a patient with AD (Lin).

Combination of FUS and Lecanemab to Improve Drug Efficacy

I hypothesize that combining lecanemab and focused ultrasound could lead to a more productive treatment plan. The combination of these two treatments could vastly improve the lives of patients with AD, and may even plateau most of their symptoms.

FUS has the potential to open up the BBB and improve drug delivery. As it stands, 10 mg per kg of body weight every 2 weeks through IV infusion is the dose of Lecanemab needed for the drug therapy to show results. Implementing FUS alongside Lecanemab during drug delivery could improve efficacy and lessen the dosage required for Lecanemab to work. Currently, the practicality of this process is being tested by Ali Rezai of West Virginia University in their clinical trial. They are testing the safety and feasibility of breaching the BBB using FUS with the combination of Lecanemab dosage (Rezai). This trial was started in July 2022, and the predicted end date is July 2029. They are still in the first stage of their trial, Early Phase 1. In this experiment, the researchers will intravenously infuse either lecanemab or aducanumab every 2 weeks, subsequently followed by the opening of the BBB (Rezai).

The potential benefits of combining FUS and Lecanemab are immense. FUS has been shown to reduce amyloid and tau in the brain and improve memory conditions for patients in the late stages of AD (Noel). Lecanemab is a specific monoclonal antibody that aims for amyloid reduction in the brain by targeting amyloid-beta as its antigen (“Lecanemab Approved …”). The coalescence of both of these treatments could improve drug efficacy and benefit the patient receiving Lecanemab because a lower dosage of the drug could be required. Without FUS, higher doses of Lecanemab might be necessary for its full function, due to the BBB preventing much of the Lecanemab from entering the brain. With the addition of FUS, a lower dose is needed for Lecanemab to work, as the BBB would be slightly breached, and more Lecanemab would be able to enter the brain. This lower dose would allow for the cost of the drug and the severity of side effects to decrease.

Future Direction of this Research

Important factors when running a new research trial on the safety and feasibility of combining FUS with Lecanemab would be to consider the presence of APOE ε4 and the stage of AD in the patient. APOE ε4 is a very critical allele that influences the onset of AD, but it can also affect the strength of the side effects of Lecanemab. Usually, Lecanemab has minimal side effects, but combined with the APOE ε4 allele, it can increase the risk of this medicine (“Lecanemab”). The stage of AD for the patient is also a substantial aspect that researchers must consider when performing an experiment like this. Lecanemab only affects patients in the mild to moderate stages of AD, so checking for that will be important for researchers (“Lecanemab Approved …”). Late stages of AD will not be compatible with Lecanemab. This trial should have four separate types of treatment: patients receiving a placebo, patients receiving Llecanemab, patients receiving FUS with microbubbles, and patients receiving a combination of both treatments. Likewise, the trial should also be double-blind.

Based on the PET scans and mini AD diagnostic tests, they could show improvement in the reduction of amyloid-beta or cognitive improvement (“Cognitive Screening and Assessment”)(“Amyloid PET Scan …”). Talking to the caregivers could also be another outcome to look at because caregivers would give an honest and unbiased opinion about the mental state of their AD patients.

Conclusion

Around 120 thousand Americans died from Alzheimer’s Disease in 2019, and the future for victims is bleak, with no cure available (“2023 Alzheimer’s…”)(Huang). Some pathological symptoms associated with this disease are amyloid-beta plaques and tau tangles (“What Causes Alzheimer’s Disease”). Thankfully, Lecanemab is a new and powerful anti-amyloid drug, with the potential to influence future drugs in the AD industry (“Lecanemab Approved…”) and in combination with FUS has been shown in clinical trials to be beneficial to AD patients (Contie)(Noel). However, an important thing to remember is that Lecanemab and FUS are both just treatments and not cures for the condition itself. In conclusion, this paper talked about the immense prospect of the combination of FUS with microbubbles with lecanemab, and the benefits of the approach outweigh the negatives (Rezai). More research into the combination of both therapies has to be conducted by scientists and researchers alike to gain further understanding of the feasibility of the process.

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