MEDICAL COLLEGE OF WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Breaking Barriers with Aducanumab: Examining Alzheimer's Treatments and Implications for Patients

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Abstract

Alzheimer's disease is a neurodegenerative disorder affecting millions of patients worldwide, yet treatment options remain limited. For years, the mainstay of treatment has been cholinesterase inhibitors to increase concentrations of acetylcholine to stabilize cognitive function. Aducanumab (Aduhelm®) is a newly approved medication that targets beta-amyloid plaques, a hallmark of the disease. However, its approval has been surrounded by controversy, ultimately leaving a consensus on the medication's efficacy in question. Excessive costs and adverse reactions associated with treatment also have significant implications for patients and their caregivers. The purpose of this piece is to review current treatment recommendations for Alzheimer's disease, focusing on the recently approved monoclonal antibodies.

Alzheimer's disease (AD) is a common type of dementia and is most prevalent in geriatric patients.[1] In 2023, the number of affected patients in the United States (US) was 6.7 million, with projections to reach 12.7 million by 2050. It is estimated that 1 in 9 US adults (10.8%) 65 years or older have AD. In 2021, the US population over 65 was 58 million, and it is expected to grow to 88 million by 2050, leading to rising concerns about effective treatment options for AD patients.[2]

Patients with AD typically present with beta-amyloid plaques. While lifestyle factors may not directly contribute to the likelihood, onset, or pathological presentation of AD, these can impact the patient's (and their caregivers') quality of life.[3] The Alzheimer's Association (https://www.alz.org) offers resources to support both patients and caregivers, including a helpline and online tools.[2] While this neurodegenerative disease has been recognized throughout history, only more recently has there been a focus on new research, specifically for medications targeting the beta-amyloid plaques.[4]

Beta-Amyloid

Amyloid proteins in the brain can produce beta-pleated sheets that are resistant to protein breakdown.[5] These proteins can be either alpha or beta subunits, but they all begin as an alpha-beta-fragment. The congregation of these fragments stimulates the formation of amyloid plaques that can be deposited in the brain. Plaque concentrations and deposition can vary among AD cases.

A 2006 University of Minnesota study started linking beta-amyloid assembly with the impairment of memory.[6] These findings spurred a new focus area in AD research, although recent reports raised concerns about data manipulation, leaving patients and healthcare providers with questions about study validity.[7]

Current Treatments

The current guidelines for the management of early AD recommend the use of cholinesterase inhibitors.[8,9] The goal of therapy is to improve or stabilize memory and cognitive function by preventing or reducing the degradation of acetylcholine through inhibition of acetylcholinesterase, thereby increasing concentrations of acetylcholine. The United States Food and Drug Administration (FDA) has approved cholinesterase inhibitors for AD, including donepezil, rivastigmine, and galantamine.

Donepezil is a reversible and noncompetitive acetylcholinesterase inhibitor; rivastigmine is a pseudo-irreversible inhibitor; and galantamine is a competitive and reversible inhibitor.[8,10-12] The choice of cholinesterase inhibitor is based on several factors, including ease of use, patient preference, cost, safety issues, and potential drug-drug interactions.[8] Acetylcholinesterase inhibitors are titrated to help with adverse effects such as nausea, vomiting, diarrhea, or constipation.[13] Adverse effects such as bradycardia and insomnia may limit their use for older adults with AD.

Due to AD's progressive nature, adjusting a patient's therapy may become necessary as part of treatment. As the benefits of the cholinesterase inhibitor decline, a next appropriate step may be the use of memantine, an N-methyl-D-aspartate receptor (NMDA) antagonist, which is approved for moderate to severe AD.[8,14] Overstimulation of glutamate may lead to excitotoxicity and neuronal cell death, and while memantine can control this, it does not affect normal neurotransmission. Memantine is slowly titrated to reduce mild adverse effects such as headache, constipation, confusion, and

dizziness, which can be problematic in older patients.[8] Memantine combined with cholinesterase inhibitors has been shown to slow the cognitive and functional decline, compared to cholinesterase monotherapy.[15] To date, studies of memantine alone and in combination with cholinesterase inhibitors in mild AD have provided insufficient evidence to support an indication for mild AD.[16]

A New Therapy: Aducanumab

Since beta-amyloid plaques are a pathophysiological feature of AD, one theory for delaying progression is to interrupt plaque formation. Aducanumab is a monoclonal antibody and an anti-amyloid medication used to reduce and decelerate the progression of AD by targeting beta-amyloid.[17] It targets the plaques by binding to soluble oligomers and insoluble fibrils to mark them for elimination by microglial cells.[18] Aducanumab differs from other immunotherapies for AD because of its selective binding and ability to target oligomers and not monomers. Beta-amyloid monomers have physiological roles in the brain, while the oligomers and plaques are thought to be potentially neurotoxic.

Aducanumab is only available by IV and has a complex dosing schedule.[19] The patient receives a 1-hour infusion every 4 weeks, with a minimum interval of 21 days, due to its long half-life of 24.8 days. The goal maintenance dose is 10 mg/kg, based on actual body weight, but this is titrated up. The first and second infusions are 1 mg/kg, the third and fourth are 3 mg/kg, and the fifth and sixth are 6 mg/kg. After the first six infusions, the patient receives the 10 mg/kg maintenance dose.

Adverse reactions to aducanumab include headache, diarrhea, falling, and altered mental status.[19] The most significant adverse reactions are amyloid-related imaging abnormalities (ARIA). These are changes in the brain seen on magnetic resonance imaging (MRI) scans. ARIA-Edema (ARIA-E) is related to cerebral edema, and ARIA-Hemosiderin deposition (ARIA-H) is related to cerebral microhemorrhages and iron deposits called hemosiderosis. Both are believed to be related to increased cerebrovascular permeability and leakage of the blood vessels. In clinical trials, ARIA-E occurred in 35% of patients receiving aducanumab and only 3% of patients receiving placebo.[17] ARIA-H occurred in 15% of patients receiving aducanumab and only 3% of patients receiving placebo. Both ARIA presentations are typically present around the initial eight infusions and generally resolve in 12 to 20 weeks.

Due to these serious adverse reactions, aducanumab therapy requires close monitoring.[19] Patients should receive a positron emission tomography scan or lumbar puncture to verify the presence of beta-amyloid plaques before initiating treatment. Patients should also receive a brain MRI before treatment and before infusions five, seven, nine, and twelve. Additional MRIs should be obtained if ARIA are suspected. Adjustments to dosing are made based on the severity of symptoms and the presence of ARIA on the MRI.

Clinical Trials

Aducanumab showed positive outcomes in transgenic mice when applied topically to beta-amyloid plaques, although systemic treatment did not show significant benefit.[20] The first human trial was a randomized, double-blind, placebo-controlled, single-dose escalation Phase I clinical trial (n = 53).[21] Patients received doses ranging from 0.3 to 60 mg/kg or placebo. Patients tolerated doses up to 30 mg/kg with some adverse effects, including headache, diarrhea, and upper respiratory infection. The most serious adverse effect was ARIA-E in patients receiving 60 mg/kg doses. Following this came a randomized, double-blind, placebo-controlled Phase Ib clinical trial, called PRIME (n = 125).[22] Patients received doses of 1 to 10 mg/kg or placebo intravenously every 4 weeks for 52 weeks. There was a decrease in beta-amyloid plaques and cognitive decline for individuals receiving 3 to 10 mg/kg doses; however, higher doses were also associated with greater instances of ARIA-E.

Two duplicate Phase III clinical trials to determine the safety and efficacy of aducanumab as treatment of mild AD started in 2015.[17] These trials were randomized, double-blind, placebo-controlled trials, called EMERGE (n = 1,643) and ENGAGE (n = 1,647). Participants received low or high target doses of 3 to 10 mg/kg or placebo intravenously every 4 weeks for 76 weeks. Primary endpoints were measured by changes in Clinical Dementia Rating Scale sum of boxes (CDR-SB), which measures cognitive decline in dementia. The EMERGE trial satisfied the primary endpoints, while ENGAGE did not. The CDR-SB results were in favor of the high-dose in EMERGE and in favor of the placebo in ENGAGE. In March 2019, the trials were discontinued after meeting their predetermined futility limits because of these discrepancies between the EMERGE and ENGAGE results.[17]

Approval and Controversy

Aducanumab was approved for the treatment of AD in patients with beta-amyloid plaques in June 2021.[19,23] This is the first new treatment for AD since 2003 and the first to directly target the pathophysiology of AD.

The medication was approved via the FDA's accelerated approval process, which is reserved for medications that treat serious or life-threatening illnesses and provide a meaningful therapeutic benefit over existing treatments.[23] Accelerated approval can be determined based on the medication's effect on a surrogate endpoint that is likely to lead to clinical benefit; however, a post-approval trial is required to verify that the medication is providing its expected benefit. For aducanumab, the surrogate marker is the beta-amyloid plaques present in AD patients.[24] This verification trial has not yet been completed.

Traditionally, the FDA has preferred two adequate and well-controlled trials to show clinical efficacy for any potential new approvals. However, in 1997, an amendment was introduced that allowed the FDA to use evidence from a single trial to approve a new medication.[25] In November 2020, an FDA statistician and an advisory committee concluded that aducanumab should not be approved, due to the contradicting trial results in the Phase III trials EMERGE and ENGAGE.[25,26]

Additionally, the sponsor and manufacturer of aducanumab worked closely with the FDA to further analyze these trials. This was seen as a highly unusual collaboration between the FDA and a sponsor and has been criticized as undermining the FDA's credibility and compromising their objectivity in approving the medication.[24] Despite these concerns, the FDA approved the medication, even

with ten of the eleven members of the FDA advisory committee advising against approval. In protest of its approval, three of the advisory committee members have since resigned, with one member calling this "probably the worst drug approval decision in recent US history."[27]

Effects on Patients

In addition to emotional stress of the disease, there are significant obstacles patients face with AD, including struggles with adherence due to increased forgetfulness, increased dependence on caregivers, and financial burdens associated with the medications and healthcare expenses.

As the disease progresses, the patient develops increased forgetfulness, which can lead to lower medication adherence, thereby creating a spiral of forgetting and disease progression. Normal techniques to increase adherence, such as bubble packs and strategic placement of medication, are not as effective in this population.[28] The biggest way healthcare providers can improve adherence in patients with AD is through family and caregivers, especially during the early onset of AD.[29]

A study looking at adherence and tolerability of AD medications found that cost, in conjunction with adverse effects, was responsible for almost 70% of patients discontinuing their medications.[30] Anticholinesterase inhibitors are $4 to $16 per pill, depending on dosage form, for an annual cost of up to $5,600.[11-14] A new medication like aducanumab is only available through IV and is roughly $340 per mL, which can cost $28,000 anuually.[19] Even if covered by insurance, any of these agents could be a financial burden.

Each medication used to treat AD has a variety of adverse effects, some of which may be serious. NMDA inhibitors can cause more confusion compared to acetylcholinesterase inhibitors, which is problematic in elderly patients.[14] Aducanumab has an increased risk for brain bleeds and swelling, resulting in a need for increased monitoring including MRIs, and potentially patient harm.[19]

Recent Updates in Therapy

Gantenerumab is a monoclonal antibody treatment similar to aducanumab in that it binds to the alpha-beta deposits and removes the beta-amyloid plaques. Like the trials for aducanumab, the study evaluating gantenerumab, SCarlet RoAD, was halted early for futility.[31] There were no observable differences between groups in this Phase III clinical trial as of November 2022. Researchers stated that gantenerumab achieved amyloid clearance in 28% and 25% of patients in the first and second Phase III trials respectively, half of what the manufacturer expected to see.[32,33]

Lecanemab (Leqembi®) is a monoclonal antibody similar to aducanumab and gantenerumab that was recently approved by the FDA through an accelerated approval process. Patients receiving treatment also showed statistically significant reductions in beta-amyloid plaques. Additionally, the rate of cognitive function decline slowed at 18 months with lecanemab versus placebo. While these results are statistically significant (p=0.00005), it is unclear whether this would be a clinically significant change in decline rate for patients.[34] These are promising results, yet the FDA only considered the phase II trials.[35] During the Phase III trial, 13% of patients developed mild to moderate brain swelling and about 17% of patients developed brain bleeding.[34]

Conclusion

Current guidelines for the treatment of AD involve the use of cholinesterase inhibitors and memantine to slow disease progression. Aducanumab is a new treatment for AD that was approved using the FDA's accelerated approval process. During this approval, the Phase III evidence was conflicting, and efficacy was focused mainly on the surrogate marker of beta-amyloid reduction versus clinical cognitive improvements. Despite the controversy of aducanumab, there continues to be heavy interest in developing new medications for AD.

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