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Updates on Disease-Modifying Therapy for Alzheimer's Dementia:

Options for Delawareans

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Introduction

Alzheimer's disease (AD) is a leading cause of dementia worldwide, characterized by progressive cognitive decline and memory loss. Over 22,000 people are living with Alzheimer's disease in Delaware alone. Up until recently, the only medications to treat Alzheimer's were cholinesterase inhibitors and memantine. Neither category of medication could alter or change the course of the illness. At best, they offered temporary, symptomatic improvement in memory and cognition. For almost 20 years, these were the only FDA-approved treatments for the cognitive symptoms of Alzheimer's. Despite years of effort and over $40 billion spent since the 1990s, treatments that could target the disease process and either halt the disease progression or slow it down remained elusive. As a geriatric psychiatrist and former fellowship program director, I would tell prospective fellows that our work involves being present for our patients and their caregivers on this journey. Much like our predecessors in other fields of medicine, what we could not offer in terms of treatment, we had to make up for with our attention and support. Imagine being a cardiologist or oncologist in the 1940s or 50s—no cardiac catheterization, statins, chemotherapy, personalized vaccines, or immunotherapy. I could only hope that one day I would be able to say to my learners, "back in the day before we had…."

Amyloid-Targeting Therapies: Breakthrough or Bust?

The focus for disease-modifying therapy for Alzheimer's disease has been on targeting amyloid, the main component of the amyloid plaques which are one of the two pathological hallmarks of Alzheimer's, the other being tau tangles. Specifically, multiple pharmaceutical companies sought to develop competing monoclonal anti-amyloid antibodies that aim to disrupt amyloid plaque formation. Despite substantial funding and many clinical trials, every anti-amyloid monoclonal antibody came up short in terms of demonstrating efficacy in altering the course of Alzheimer's disease in clinical trials. That seemed to change with aducanumab, which received FDA approval in 2021 via an accelerated approval pathway based on efficacy on the surrogate endpoint of amyloid clearance and not clinical efficacy. This decision was not without controversy given the lack of evidence that aducanumab improved outcomes for patients and its high cost of $56,000 annually. Perhaps it was this tenuous beginning that doomed aducanumab, as it was discontinued by Biogen two years after approval due to low sales and lack of insurance coverage.

After the demise of aducanumab, hope seemed to spring eternal with the approval of lecanemab in 2023 and donanemab in 2024. Both demonstrated some slowing of cognitive decline, although the effect for both was modest. Neither agent improved cognition. Practically speaking, the benefits of these medications for patients were an additional 8-13 months of independence compared to patients not on treatment.[1] For patients facing the devastating loss of memory and functioning, this can still be meaningful. However, this year of delay is not without risk or burden.

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The Long and Winding Path of Anti-Amyloid Therapy

Pursuing anti-amyloid therapy is not for the faint of heart. To begin with, only patients with early/mild disease are candidates for anti-amyloid therapy. Patients must have a diagnosis of either mild cognitive impairment (MCI) or early Alzheimer's disease, for which most programs require confirmation with neuropsychological testing. In other words, patients with the greatest levels of functional and cognitive impairment are not eligible to receive treatment due to a lack of efficacy in such advanced patients. Furthermore, a diagnosis of MCI or early/mild Alzheimer's is not a guarantee that a patient can receive treatment.

Prospective patients must have either an amyloid PET or spinal tap to confirm the presence of amyloid in the brain. Also, patients require a brain MRI to rule out the presence of pre-existing vascular disease and must undergo genetic testing to determine APOE 4 carrier status. Screening MRIs and genetic testing are vital in assessing the risk of developing the main side effect of these agents, amyloid-related imaging abnormalities (ARIA).

ARIA can appear as either ARIA-E (edema) or ARIA-H (hemorrhage). Patients who are homozygous for APOE 4 have higher rates of ARIA compared to APOE 4 heterozygotes or non-carriers. For donanemab, the rates of ARIA-E in clinical trials were 41.7% for homozygotes, 21.5% for heterozygotes, and 11% for non-carriers respectively.[2] Rates of ARIA-E in lecanemab trials were 34.5% for homozygotes, 11.6% for heterozygotes, and 6.5% for non-carriers.[3] Patients with significant pre-existing cerebrovascular disease (including microhemorrhages) were excluded, further limiting generalizability to the broader population living with Alzheimer's dementia. While ARIA can be mild and asymptomatic, in its severest forms, ARIA can mimic a stroke and lead to life-altering complications or even death. Patients who develop symptoms of ARIA must go to an emergency room immediately and have a stat MRI to properly diagnose ARIA. Also, such patients need to carry a card to give to ER staff informing them that unlike other patients with symptoms consistent with a stroke, thrombolytic therapy is contraindicated in patients receiving anti-amyloid therapy. Patients must also discontinue monoclonal antibody treatments for any other health conditions, and the use of anticoagulants is exclusionary.

For patients who make it through the screening process and are eligible, treatment lasts 12-18 months. Both medications are administered via IV infusion, every two weeks for lecanemab and every four weeks for donanemab, and require frequent brain MRIs to monitor for the emergence of ARIA. The risk of ARIA appears greatest in the early phase of treatment. Patients are strongly discouraged from travel during at least the first six months of treatment given the unpredictable nature and potentially sudden onset of ARIA symptoms.

Being Realistic

For patients, families, and clinicians exploring the possibility of pursuing anti-amyloid therapy, it is crucial that everyone involved adopt an attitude of caution and patience. Patients need to have a strong support system to help with transportation to the multitude of appointments, keep track of scheduling, and help watch for the development of ARIA or other side effects. The screening process is involved and complicated. A helpful comparison for patients and families is to think of this almost as if one were entering a clinical trial, with its myriad of screening assessments, long list of exclusions, and intensive monitoring and follow-up. While the risks are significant and benefits modest, patients who choose to be pioneers in the field of disease-modifying therapies

for Alzheimer's disease are laying a path not just for themselves but for future patients as well. Just as past generations endured the toxicity and perils of early chemotherapeutic medications for cancer, today's patients are navigating a field still in its infancy. One must hope that the treatments we have today pale in comparison to what the future will offer.

ChristianaCare's Swank Memory Center is providing anti-amyloid therapies for patients living with Alzheimer's and MCI in Delaware. Dr. Huege may be contacted at steven.huege@christianacare.org.

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