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Commentary

A Watershed for Alzheimer's?

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Alzheimer's disease (AD) is the leading cause of dementia in the world [1]. Approximately 6.7 million people in the U.S. over 65 have AD, and it is estimated that as many as 13.8 million will have the disease by 2060 [2]. There are no therapies that reverse AD, and until recently, there were no disease-modifying therapies. So, how well do we understand the disease mechanism for AD? What therapies show promise? What are the major challenges facing clinicians and research scientists in terms of diagnosis and effective therapies for this dreaded disease? This brief commentary asks if the advances made in recent years will mark a turning point in the treatment of AD.

Since the 1980s, our major understanding of the disease mechanism of AD has come from the amyloid hypothesis [3]. This idea firmly associates plaques-forming β-amyloid peptides with neural inflammation and neuronal cell death. The progress of the disease leads to progressive memory loss due to degeneration of specific brain loci, usually starting with the entorhinal cortex and hippocampus. As the disease progresses, many other areas of the brain undergo atrophy leading to a further decline in cognitive function. Most evidence indicates that amyloid plaque buildup initiates the hyperphosphorylation of the tau protein, which is normally involved in the stabilization of neuronal microtubules [4]. Tau hyper-phosphorylation leads to neurofibrillary tau tangles that inhibit neuronal transport and are toxic to the nerve cell. Neuron cell death ensues. Although other hypotheses have challenged the amyloid hypothesis, it remains the predominant theory at present [3].

Until recently, the main therapy for AD involved the use of cholinesterase inhibitors [5]. This approach reduces the degradation of acetylcholine, a neurotransmitter involved in memory and associated skills. These inhibitors have been found to slightly delay loss of brain function in patients with mild to moderate AD [6]. However, cholinesterase inhibitors can cause side-effects such as dizziness, nausea and vomiting. The outcome from long-term treatment with these drugs is unclear, and this therapy is not disease-modifying.

The latest treatment for AD, derived from the amyloid hypothesis, utilizes monoclonal antibodies (MABs) directed at β-amyloid [7]. The strategy for this approach is to remove amyloid plaques with the expectation that neuronal death will be impeded. Although this therapy does not reverse the course of AD, several MABs have been effective, to a small extent, in slowing the progression of the disease in the incipient stages of dementia known as mild cognitive impairment (MCI). The current therapies approved by the FDA are Kisunla ([8], donanemab-azbt, Eli Lilly), and Leqembi ([9], lecanumab, Eisai and Biogen). The first of the anti-amyloid vaccines was Aduhelm ([10], aducanumab, Eisai and Biogen) which has been discontinued, effective November 1, 2024, so that efforts can focus on Leqembi. These drugs are by no means a game changer. Besides only having a small effect on the early symptomatic stages of the disease, there are serious risks, including swelling or bleeding in the brain [11]. They are also expensive: a one -year supply of Leqembi is $26,000, and Kisunla is $32,000. However, the appeal for Kisunla is that once the target (i.e. amyloid plaques) is removed, dosing can be stopped, whereas dosing with Leqembi must be continued. Depending on a patient's health care plan, there can be partial coverage for the cost of these drugs [12]. The decision rests with the individual. Some patients may find the small effect on cognitive decline, and physical risks worthwhile if it makes a difference in their daily tasks.

The small effect on cognitive decline by these MABs suggests that the accumulation of tau tangles is diminished. Indeed, a post hoc analysis from a Leqembi tau-Pet sub study indicated that tangle accumulation was stopped during the course of the study [13]. This indicates that tau-tangle accumulation prior to MAB administration was not affected by Leqembi, a probable reason for the slight effect on cognition. A clinical prevention study is planned for late 2024 using Leqembi with an anti-tau antibody on a cohort with dominantly inherited AD [14].

One of the major challenges in developing an effective AD therapy is to devise a diagnostic test for the incipient stages of the disease where therapeutic intervention may be more effective. The diagnosis of AD is difficult and usually entails the use of tests that measure a person's cognitive abilities as well as reliable pharmacologic tests. Cognitive tests are usually difficult to interpret, whereas an easily interpreted laboratory test would be of enormous value. Early on, the only way of determining if a person had AD was by post-mortem analysis of brain tissue. Since that time, diagnostic advances have been made in a number of areas [15]. These include structural imaging technologies like magnetic resonance imaging (MRI) and computed tomography (CT) that can provide information on the atrophy of specific areas of the brain. Functional imaging techniques have been developed that involve positron emission tomography (PET) and functional MRI (fMRI) which can measure the utilization of oxygen and sugar by specific brain loci. Another modality employs molecular imaging by PET to detect amyloid plaques and tau by using specific ^{18}F-labeled radiotracers. Cerebral spinal fluid analysis of tau and β-amyloid may be used to diagnose AD in its early stages [16]. Very recently, a blood test has been developed that examines two types of β-amyloid and a variant of tau called p-tau217 [17]. The accuracy of the test was 88-92% with p-tau217 by itself giving similar results. Currently, developments on the diagnostic front look very encouraging and more advances may bring us closer to the diagnosis of the disease in its earliest stages.

So, are we nearing a watershed in reversing the course of AD? Considering the limited effectiveness of our newest therapies, not yet. Still, the advances in diagnostic technologies are encouraging and may pave a way to detecting earlier stages of the disease where current MAB therapies or other approaches might be more effective. And although much of the science regarding the amyloid hypothesis is solid, there are gaps that need to be filled in [3]. Alternative hypotheses that have some scientific rigor should also be considered. Oftentimes, an idea coming out of left field can offer a turning point. If the science has a solid foundation, we ignore it at our peril.

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