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Food and Drug Administration Accelerated Approval of Lecanemab for Early Alzheimer's Disease—Hope, Reality, and the Unknown Going Forward

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Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by cognitive impairment, behavioral changes, and functional decline. Aging remains the largest risk factor for late-onset AD. An additional factor may be a systemic failure of cell-mediated amyloid β (Aβ) clearance, which contributes to AD onset and progression.[1,2]

Alzheimer's disease is the most prevalent form of age-related dementia in the world. By 2050, there will be 115 million people (10%–30% of the population 65 years or older) with AD. The pathophysiology of AD is complex and characterized by Aβ plaque deposits and neurofibrillary tangles formed by hyperphosphorylated tau proteins. Evidence suggests that AD begins decades prior to diagnosis and functional decline.[2]

RESEARCH PAST AND PRESENT

Over the past 30 years, research has been built on an amyloid cascade hypothesis; if the Aβ is removed, this should cure AD. Agents tested include those that either lowered Aβ, prevented Aβ accumulations, or eradicated Aβ deposits. So far, there are still no preventive or curative treatment options for AD.[2,3]

Recent research has focused on development of monoclonal antibody therapies that target Aβ plaque formation and removal based on the theory that AD is the systemic failure of cell-mediated Aβ clearance.[3] This accumulation of soluble and insoluble aggregated Aβ appears to initiate and potentiate pathologic processes in AD driving disease progression.[3,4]

The January 6, 2023, news of the accelerated Food and Drug Administration (FDA) approval of lecanemab (Leqembi; Eisai R&D Management Co, Ltd, Tokyo, Japan) for AD was exciting news. Lecanemab is the second drug approved that targets the pathophysiology of AD and is administered by intravenous infusion approximately every 2 weeks in early AD.[5] This humanized γ1 (immunoglobulin G1) monoclonal antibody binds and eliminates Aβ protofibrils, which appear to slow progression of the disease and may be more efficient than the first product approved in this new drug class—aducanumab (Aduhelm; Biogen, Cambridge, Massachusetts). Aducanumab was also approved via FDA-accelerated approval in June 2021 for removing plaque.[6,7] The accelerated approval pathway is used to approve drugs for serious conditions where therapy is lacking, and early evidence suggests that the drug is likely to provide a clinical benefit.[8]

The FDA's decision followed the early release of phase III clinical trial results published in the *New England Journal of Medicine*.[4] In this clinical trial (NCT03887455), lecanemab reduced markers of amyloid in early AD and resulted in moderately less decline on measures of cognition and function compared with placebo at 18 months. Lecanemab was also associated with significant adverse events; 26.4% of subjects experienced infusion-related reactions including nausea, vomiting, and changes in blood pressure, and 12.6% experienced imaging abnormalities.[4]

Amyloid-related imaging abnormalities (ARIAs) have occurred with use of aducanumab and lecanemab. Amyloid-related imaging abnormality generally presents as temporary swelling in areas of the brain that usually resolve over time. Swelling may also correspond with small areas of bleeding inside or on the surface of the brain. Symptoms

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The author reports no conflicts of interest.

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DOI: 10.1097/NUR.0000000000000745

of ARIA may include headache, confusion, dizziness, vision changes, nausea, and seizures. Although symptoms of ARIA are rare, serious and life-threatening outcomes may occur.[6]

PRESCRIBING CONSIDERATIONS

The FDA approvals of aducanumab and lecanemab have provided hope for AD patients and their families. However, the favorable effects on cognition are small. Minimized serious safety concerns coupled with exaggerated benefits in the media have created additional tensions in the provision of care. What is brewing is a "perfect storm" for clinicians that consists of false hopes for patients and families, pressure on clinicians to provide drug access, and funding that is scarce at best.[9]

Considerations regarding therapy should begin with careful examination of the risks and benefits with the patient and family. Although lecanemab did clear amyloid from the brain and there was a significant favorable effect on cognitive decline, the effect was small.[4,5] In addition, subject selection in the trial was highly selective with deep exclusion criteria. The study sample does not reflect the general population of older adults usually with multiple comorbidities in addition to AD. Clinicians must ask: Are these early findings clinically significant? Also, prescribers must consider that the rapid FDA approval of lecanemab was based on biomarkers and not clinical benefits.[9,10] Finally, the burden associated with treatment and ongoing monitoring for the patient, family, care provider, and healthcare organization cannot be overstated.[10]

The safety profile is still being written for lecanemab. Similar to other antiamyloids, safety concerns of brain edema, asymptomatic brain hemorrhage, and long-term effects are unknown. Although the number of deaths for treatment and control groups was comparable, 6.9% (compared with 2.9% in the placebo group) experienced adverse effects severe enough to leave the trial.[4,9] Consider too that some patients may accept the risk of sudden death with treatment compared with facing a drawn-out decline over many years due to AD. However, for families, this could mean fewer years with the patient while the effects of AD are mild.[10]

Aducanumab and lecanemab therapy is expensive. Even technology-rich healthcare systems may not be able to provide all the elements needed for a course of therapy.[9] Patients with cognitive impairment need to be identified early in their disease course with confirmation of amyloid status with biomarkers. The problem is, at this time, amyloid positron emission tomography scans are not covered by Medicare or private insurers. Additional competencies are required for clinicians and radiologists to provide lecanemab and monitor for adverse effects. Infusion centers associated with neurology practices are recommended to provide long-term infusion lecanemab therapy that requires intravenous administration every 2 weeks for 18 months.[10]

SO WHAT ABOUT NOW?

During the past 3 years, aducanumab and lecanemab have demonstrated significant clearance of cerebral Aβ deposits.[11,12] Lecanemab is recommended for patients with mild cognitive impairment or early stage of disease like the population in recent clinical trials. For now, there are no safety or effectiveness data for beginning treatment at earlier or in later stages of AD.[11] More research is necessary regarding the benefit (magnitude of the slowing of cognitive decline) and risk (edema and cerebral hemorrhage) associated with these drugs.[12]

Although research continues with lecanemab, there are other interventions available now that can help patients with mild AD. First, screen and treat anxiety and depression and consider discontinuing anticholinergic medications including any over-the-counter medications and sleep aids. Screen for hearing loss and obstructive sleep apnea. Consider intensive blood pressure control to systolic blood pressure ≤120 mm Hg based on current guidance.[10] These interventions may help improve cognition and provide improvement in quality of life.

THE FUTURE

Alzheimer's disease is a global health crisis. Agents are needed to prevent AD, delay the onset of AD, slow the progression of AD, improve cognition in AD, and reduce behavioral disturbances associated with AD. As of January 2022, there were 143 agents in 172 clinical trials for AD in the United States that include disease-modifying therapies (83.2%), cognitive enhancing (9.8%), and treatment of neuropsychiatric symptoms (6.9%). Advances in drug design, outcome measures, and biomarker use promise to accelerate the future delivery of effective agents.[13]

There is also hope from this research for persons with some types of Down syndrome (DS). Down syndrome is caused by trisomy of chromosome 21, which leads to a propensity to develop Aβ brain pathology usually in early adulthood, which can be followed later by cognitive and behavioral deterioration. Learning the mechanisms surrounding Aβ pathology in AD research is helping to better understand the clinical situation of DS individuals and may help to identify interventive strategies. Early data suggest that lecanemab may have the potential to preserve cognitive capacity in DS.[2,14] Finally, current work is also evaluating the efficacy of subcutaneous administration of lecanemab and if lecanemab can prevent the onset of dementia in persons with amyloid pathology with no overt clinical symptoms.[5]

Patients younger than 65 years with vascular risk factors are also at increased risk of late-onset AD. There are healthy lifestyle choices that may reduce risks for AD from population-based studies. Leisure activities, physical exercise, and a Mediterranean diet may be protective against AD. There is also hope from recent large population-based longitudinal epidemiological studies that the prevalence of

dementia may be decreasing in Western countries. Hopefully, we will find in the future that a significant proportion of AD cases are preventable.[15]

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