EDITORIALS

Progress with Treatments for Alzheimer's Disease

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An estimated 50 million people worldwide have dementia, mostly due to Alzheimer's disease. The inexorable progression of Alzheimer's disease exerts a huge toll on patients, families, and society, costing approximately $1 trillion annually, an amount that is likely to increase with the growing number of elderly people. It is no surprise that Alzheimer's disease is among the most feared diseases of aging. Hence, there is widespread interest as new clinical trial results are reported, but also much angst given all the trial failures to date. This issue of the *Journal* provides some tentative hope with the results of TRAILBLAZER-ALZ, a phase 2 clinical trial of donanemab, an antiamyloid monoclonal antibody, in early Alzheimer's disease.[1]

In this trial, 257 participants with early Alzheimer's disease were randomly assigned to receive donanemab or placebo intravenously every 4 weeks for approximately 1.5 years. The prespecified primary outcome goal was met: treatment with donanemab resulted in 25 to 30% less decline than placebo in the score on the Integrated Alzheimer's Disease Rating Scale, a composite measure of cognition and the ability to perform instrumental activities of living. Although encouraging, these findings, which amounted to a 3-point difference on a scale ranging from 0 to 144, barely showed significance ($P=0.04$), and the clinically relevant secondary outcomes of dementia severity, cognition, and functional abilities all failed to show treatment effects. Nevertheless, the results warrant further study of donanemab.

Disease-modifying treatments for Alzheimer's disease have mostly targeted the amyloid plaques that are a hallmark of the disease, but repeated trial failures have led many to question this choice of target. Interventions aimed at amyloid have included β- and γ-secretase inhibitors to decrease amyloid-β (Aβ) production, drugs to prevent Aβ aggregation, and active and passive vaccines to facilitate Aβ clearance. Until recently, trials testing these drugs have been unsuccessful, with all the drugs showing no evidence of efficacy and some even worsening the clinical condition.[2] Although failing to show clinical benefit, antiamyloid antibodies targeting various forms of Aβ have led to clearance of Aβ and reduction of amyloid plaques.[3] Donanemab targets a pyroglutamate-modified, N-terminally truncated Aβ epitope that is specific to amyloid plaques and facilitates Aβ removal even after plaque formation.[4] In this trial, donanemab reduced neuritic plaque binding of a positron-emission tomographic (PET) radiotracer by 85%, normalizing levels in 68% of participants.

The trial has implications for other antiamyloid monoclonal antibodies, including aducanumab, for which a regulatory decision by the Food and Drug Administration is anticipated in June 2021. Treatments for Alzheimer's disease will require a transformation of health care practice. Early and specific diagnosis is an essential first step, because a treatment benefit is expected only when treatment is started at the very early stages of disease. Many people with dementia never receive a diagnosis of the underlying cause or receive one only after many years of symptoms.[5] In the absence of effective treatments,

evidence to support screening for dementia has been considered "insufficient" by the U.S. Preventive Services Task Force.[6] The Medicare Annual Wellness Visit was introduced to help address this deficiency; however, even with reimbursement for the assessment, its adoption in practice has been low,[7] and some studies suggest that such visits have little effect on the diagnosis of dementia.[8]

If antiamyloid treatments are shown to be successful, precise staging of Alzheimer's disease may be required. In this trial, PET scans were used to quantify both plaques and tangles in order to stringently select participants with Alzheimer's disease in the earliest stages. These narrow indications will restrict eligibility for treatment, and requirements for confirmation by biomarker testing may pose additional barriers. In the trial, only 1 in 10 screened participants met the enrollment criteria. The adverse events of amyloid-related imaging abnormalities occurred in more than one third of participants who were treated with donanemab, and future treatments may require monitoring with magnetic resonance imaging. The high prevalence of Alzheimer's disease, the shortage of specialists in the field of dementia disorders, and the expense and availability of biomarker testing for diagnosis and staging all pose challenges in the implementation of disease-modifying treatments for Alzheimer's disease.

In addition, there is a risk that health care disparities would worsen with the implementation of these treatments. Black and Hispanic or Latino people are disproportionately affected by Alzheimer's disease,[9] yet they are less likely to receive timely diagnosis and treatment than people of other racial or ethnic backgrounds.[10] The underrepresentation of minorities in Alzheimer's disease research also raises serious concerns. For example, Black patients with Alzheimer's disease may have lower tau levels than non-Hispanic White patients,[11] which poses a risk of false negative diagnosis and underestimated staging for Alzheimer's disease among Black patients. The safety and efficacy of new treatments in minority populations is impossible to know, given how few have participated in clinical trials; only approximately 3% of participants in this trial were Black and 1% Asian.

This trial of donanemab provided encouraging results that support a potential role for amyloid immunotherapies for mild Alzheimer's disease. However, the need for additional research has never been clearer. Much remains to be discovered about how to translate research into clinical practice with treatments for Alzheimer's disease that are widely available.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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