Aducanumab reduces Aβ plaques in Alzheimer's disease

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Aducanumab Reduces Aβ Plaques in Alzheimer's Disease

Sevigny J, Chiao P, Bussiere T, et al. The antibody aducanumab reduces Abeta plaques in Alzheimer's disease. Nature 2016;537:50-56.

Parkinson's disease is the second most prevalent neurodegenerative disorder next to Alzheimer's disease (AD). AD is an age-related disease that is characterized with a high prevalence of neuropathological hallmarks such as beta-amyloid, hyperphosphorylated tau, extraneuronal senile plaques, and intraneuronal neurofibrillary tangles.[1,2] There is a hypothesis that amyloid–β (Aβ) toxicity results in synaptic dysfunction and neurodegeneration that leads to declines in cognitive function associated with AD. Although prior attempts to address this hypothesis and develop treatments for reducing Aβ have not been successful, Sevigny and colleagues[3] have re-visited the hypothesis using abucanumab.

In a study published in *Nature*,[3] the authors used a double-blind, placebo-controlled phase 1b study. Abucanumab was investigated in 1, 3, 6, or 10 mg/kg doses during a 1-year period. Intravenous infusion of drug or placebo occurred monthly. A total of 165 patients were randomized and treated at 33 sites, and patients were either prodromal or mild AD with a visually positive Aβ positron emission tomography scan. At study completion, 40 discontinued treatment and 125 completed the study. Of the patients that discontinued, 20 were because of adverse events and 14 were because of consent withdrawal. The percentage of patients who discontinued was 25% of placebo group compared with 23%, 19%, 17%, and 38% of the 1, 3, 6, and 10 mg/kg aducanumab dose groups, respectively. In the completed sample of participants, there were several key findings. First, the authors found that amyloid plaques were significantly reduced with aducanumab compared with placebo at both 26 weeks and 54 weeks for the 3, 6, and 10 mg/kg doses. Second, the level of amyloid plaque reduction scaled across dose level with the greatest reduction at the highest dose. Third, the Clinical Dementia Rating–Sum of Boxes and Mini Mental State Examination were improved at 52 weeks for the highest dose of 10 mg/kg group compared with placebo. Of the reported adverse events, the main safety and tolerability finding was related to amyloid-related imaging abnormalities that occurred in a dose-dependent manner. Of the 27 patients who developed amyloid-related imaging abnormalities vasogenic oedema, 56% continued treatment and the remainder withdrew.

The findings provide evidence that aducanumab penetrates the brain and decreases amyloid plaques in patients with AD during a 54-week period. Because the amyloid reduction was dose-dependent, this provided strong evidence that aducanumab altered amyloid plaques in the brain of humans with prior evidence of a positive amyloid scan. These findings also bear on the field of Parkinson's disease. For example, this study shows the importance of having an imaging marker in Parkinson's disease that can be used to assess a potential therapy. Furthermore, about 15% to 20% of patients with Parkinson's disease with dementia have Aβ pathology, with Aβ retention mainly in the cortical and striatal regions.[4] It has been shown that those Parkinson's disease patients with Aβ deposition are at an increased risk for development of dementia.[5] We will continue to learn more because there are ongoing phase 3 clinical trials that will further test the amyloid hypothesis as a viable treatment for AD. If these phase 3 trials are successful, then future studies may also consider testing this drug in Aβ-positive Parkinson's disease. ■

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