Solanezumab Fails to Slow Cognitive Decline in Mild Dementia

Solanezumab did not significantly decrease cognitive decline in patients with mild dementia due to Alzheimer disease.

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January 14, 2019 – Intravenous infusions of 400 mg of solanezumab did not significantly slow cognitive decline in patients diagnosed with mild dementia due to Alzheimer disease, according to the results of the EXPEDITION3 trial.

Lawrence S. Honig, MD, PhD, with the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, and colleagues reported their findings in the January 25, 2018, issue of *The New England Journal of Medicine*.

Solanezumab, a humanized monoclonal antibody, was designed to increase clearance of soluble amyloid-beta (Aβ) from plasma and subsequently from the brain. In the prior EXPEDITION and EXPEDITION2 clinical trials, secondary analysis of patients with mild Alzheimer who were treated with solanezumab showed less cognitive and functional decline by approximately 34% and 18%, respectively, compared with patients treated with placebo. The EXPEDITION3 trial tested the hypothesis that reducing free Aβ might lessen the deposition of Aβ plaques and fibril clusters that characterize Alzheimer's disease.

In the double-blind, phase 3 EXPEDITION3 trial, 2129 patients were randomly assigned to receive either 400 mg of solanezumab or placebo once every 4 weeks for 76 weeks. Participants met the diagnostic criteria for probable Alzheimer disease, based on Mini-Mental State Examination (MMSE) score and biomarker evidence of amyloid-related disease.

The primary efficacy measure was the change in the Alzheimer's Disease Assessment Scale (ADAS) score of 14 items from baseline to 80 weeks. Secondary efficacy measures included scores on several assessments, including the MMSE, Functional Activities Questionnaire, and Integrated Alzheimer's Disease Rating Scale.

Of the 1822 patients who completed the trial, the mean change in the ADAS-cog14 score did not differ significantly between the solanezumab and placebo groups at week 80 (6.65 vs 7.44; difference, -0.80; 95% CI, -1.73 to 0.14; $P = .10$).

Because of the failure to achieve significance with the primary outcome, the prespecified secondary endpoints were considered descriptive and reported without significance testing. The change in the MMSE score from baseline was -3.17 for the solanezumab group and -3.66 for the placebo.

Adverse events were similar between groups. Edema or effusion lesions occurred in 1 case in the solanezumab group and 2 cases in the placebo group.

Given that the EXPEDITION3 trial did not show a benefit on the primary outcome or reproduce the promising secondary analyses of previous trials, "the rationale for further trials with solanezumab with different doses and timing may require examination," Dr Honig and colleagues concluded.

M. Paul Murphy, PhD, of the Department of Molecular and Cellular Biochemistry and the Sanders-Brown Center on Aging, University of Kentucky Medical Center, noted in an editorial accompanying the article that "although it may not quite be time to give up on Aβ immunotherapy for treating Alzheimer's disease, it would be foolish to ignore the continued failures of antiamyloid approaches."

The study was sponsored by Eli Lilly.

New England Journal of Medicine. Published January 25, 2018.