Solanezumab No Better Than Placebo in Alzheimer's Disease

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November 5, 2018 - Solanezumab does not slow cognitive decline in patients with mild Alzheimer's disease, compared with placebo, a phase 3 trial showed.

Lawrence S. Honig, MD, PhD, professor of neurology at Columbia University Medical Center, New York, and colleagues, reported their findings in the January 25, 2018, issue of *The New England Journal of Medicine*.

The amyloid beta (Aβ) hypothesis of Alzheimer's disease pathogenesis proposes that early disease results from a surplus of Aβ. This surplus leads to the formation of oligomers, fibrils, and Aβ plaques, which are a feature of established disease. Solanezumab is a humanized immunoglobulin G1 monoclonal antibody that binds to free Aβ, reducing plasma concentrations and potentially increasing clearance of cerebral Aβ.

In two previous phase 3 trials, solanezumab did not significantly reduce cognitive and functional decline in patients with mild-to-moderate Alzheimer's disease compared with placebo. However, secondary analyses showed that solanezumab did reduce decline in mild disease. This latest trial aimed to investigate the secondary analyses from the earlier trials. Researchers postulated that solanezumab would result in slower cognitive decline than placebo in mild disease.

A population of 2129 patients with mild Alzheimer's disease and biomarkers of cerebral Aβ deposition were recruited. The patients were randomly assigned to receive either 400-mg intravenous solanezumab or placebo every 4 weeks for 76 weeks. The cognitive subscale of the Alzheimer's Disease Assessment Scale was used to measure the change in cognitive impairment over 80 weeks.

After 80 weeks of treatment, the mean change in the solanezumab group was 6.65 (on a scale up to 90, where higher scores indicate a higher degree of cognitive impairment), while the change in the placebo group was 7.44. No significant difference was recorded between the groups (P = .10). Additionally, solanezumab exerted less clinical effect on cognitive decline in this study compared with secondary analyses in the previous studies.

In the solanezumab group, 84.5% of patients (*n* = 1054) had at least 1 adverse event compared with 83.4% in the placebo group (*n* = 1067). Vitamin D deficiency, nasal congestion, spinal osteoarthritis, and dysuria occurred significantly more frequently in the solanezumab group. No significant differences were recorded between the groups with regard to serious adverse events or to Aβ-related abnormalities on imaging.

Researchers proposed four possible reasons for the results: decreased peripheral free Aβ alone may not be sufficient to slow cognitive decline; the dose of solanezumab used in the study may have been clinically insufficient; the disease may eventually become non-responsive to treatment; or Aβ may not be the cause of the disease.

“The amyloid hypothesis will need to be considered in the context of accruing results from this trial and other clinical trials of anti-amyloid therapies” the study authors concluded. They proposed, “the rationale for further trials with solanezumab with different doses and timing may require examination.”

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Reference: Honig LS, Vellas B, Woodward M, et al. Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease. *N Engl J Med*. 2018;378(4):321-330. doi:10.1056/NEJMoa1705971