Two anti-amyloid antibody drugs aimed at reducing plaque buildup in Alzheimer’s disease (AD) patients failed to show benefits in clinical trials, disappointing researchers who have hoped that the anti-amyloid approach might provide a much sought-after breakthrough in AD. Findings on the two drugs were published Jan. 23 in The New England Journal of Medicine.

The two drugs, bapineuzumab and solanezumab, were each tested in two large clinical trials of patients with mild-to-moderate Alzheimer’s disease. Overall, neither drug was found to have a positive effect on patients’ cognition or functional ability when compared with a placebo treatment.

In the case of solanezumab, the researchers said that study results suggest that the drug could help patients with mild Alzheimer’s disease, and clinical trials are under way to test that hypothesis.

“These studies, although disappointing in terms of clinical outcomes, do provide important information that already is being incorporated into future research,” Stephen Salloway, MD, professor of neurology and psychiatry in the Warren Alpert Medical School of Brown University and lead author on the article about bapineuzumab, told Neurology Today. “One positive was that we did find some evidence of target engagement,” meaning that certain measures suggested that the antibody had some effect on amyloid.

But David S. Knopman, MD, professor of neurology at the Mayo Clinic in Rochester, MN, said he did not find much to be encouraged about in the published findings on the two drugs.

“In my opinion they were both negative studies that failed to show benefits based on pre-specified outcome measures,” Dr. Knopman told Neurology Today.

Dr. Knopman, who served on the data safety monitoring board for the EXPEDITION trials, which involved testing of solanezumab, said he believed these latest results “provide more support for suspending trials of anti-amyloid immunization therapy in symptomatic Alzheimer patients,” but added there could be a role in asymptomatic individuals.

THE DATA: SOLANEZUMAB
Solanezumab was compared with a placebo in two trials involving a total of 2,052 patients with mild-to-moderate Alzheimer’s disease. The participants received either 400 mg of the drug or a placebo intravenously every four weeks for 18 months. The primary outcomes measures were the changes from baseline to the end of the study on the 11-item cognitive scale, the Alzheimer’s Disease Assessment Scale (ADAS-cog 11) — with scores ranging from 0 to 70 and higher scores indicating more impairment — and the Alzheimer’s Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL), with a range of 0 to 78, with lower scores indicative of poorer functioning. After data from the first trial, called EXPEDITION 1, was analyzed, the primary outcome for the EXPEDITION 2 trial was revised to include changes in scores of a 14-item ADAS-cog 14 in patients with mild disease, which is thought to be more relevant for assessing people with earlier-stage Alzheimer’s.

“Neither study showed significant improvement in the primary outcomes,” the researchers concluded. In addition, “the current studies failed to show treatment effects on hippocampal or total brain volumes or on amyloid accumulation” on PET scan. The investigators reported, however, a positive sign — that measures of biomarkers, including plasma CSF levels of antibody, are consistent with “target engagement of soluble brain amyloid by solanezumab.”

There was slightly more edema, 0.9 percent compared with 0.4 percent, among the drug treatment group compared with placebo, and hemorrhage rates were 4.9 percent and 5.6 percent, respectively.

An editorial accompanying the studies stressed that despite the negative outcomes from the trials “overall there are enough data to support a beneficial treatment effect.” It noted that the two sets of trials provided critical pieces of information that would help inform future studies. For one, about 25 percent of participants with mild disease tested negative for amyloid on PET imaging, meaning they likely had another type of dementia rather than Alzheimer’s.

“In EXPEDITION 3, positivity on PET amyloid is an inclusion criteria, and this will greatly increase the potential to show efficacy,” wrote the editorialists Eric Karran, PhD, director of research strategy at Alzheimer’s Research UK, and John Hardy, PhD, professor of neuroscience at University College London.
THE DATA: BAPINEZUMAB
Bapineuzumab was tested in two phase 3 multicenter trials of patients with mild-to-moderate Alzheimer’s disease, including 1,121 carriers of the apolipoprotein E 4 (APOE4) gene, which is associated with a higher risk for Alzheimer’s, and 1,331 patients who were non-carriers.

Every 13 weeks for 78 weeks, study participants were given either an intravenous infusion of bapineuzumab or a placebo, with dosage dependent on body weight.

The primary outcome measures were scores on ADAS-cog11, and the Disabilities Assessment for Dementia (DAD) — with scores ranging from 0 to 100, and higher scores indicating less impairment. Baseline measurements were compared with those obtained at the end of 78 weeks. Secondary outcomes measures included findings on positron-emission tomographic imaging and cerebrospinal fluid phosphorylated tau (phospho-tau) concentrations.

“We found no significant differences between the bapineuzumab groups and the placebo groups with respect to primary endpoints or other clinical end points,” the researchers reported. The

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major safety finding was amyloid-related imaging abnormalities with edema among patients receiving bapineuzumab, especially in those on higher doses and APOE carriers.

In terms of secondary outcome measures, the study found a reduction in phospho-tau concentrations in the spinal fluid of APOE carriers getting bapineuzumab, which researchers believe may be an indication that less neurodegeneration was occurring. Also, PET scans of carriers who received the drug showed less evidence of amyloid buildup.

Dr. Salloway said both findings suggest that the antibody therapy was having some effect on amyloid, even if a clinical benefit was not apparent. He and his research team said the antibody therapy might work better at an earlier stage of Alzheimer’s.

“Amyloid accumulation probably starts many years before the onset of symptoms, and anti-amyloid treatment only after dementia develops may be too late to affect the clinical course of the disease,” the researchers wrote.

THE FINDINGS ‘IN CONTEXT’
Norman Relkin, MD, PhD, associate professor of neurology at Weill Cornell Medical College told Neurology Today, there were nuances in the findings that need to be considered.

“I think in terms of interpreting where we go from here and the meaning...
of these results, we have to consider the overall negative findings in context,” Dr. Relkin said. “The results don’t mean that there is not a future role for immunotherapy for treating Alzheimer’s and they do not mean that amyloid is not a therapeutic target. The challenge is to find the right drug, the right timing, the right dosing.”

Rachelle S. Doody, MD, PhD, professor of neurology and director of the Alzheimer’s Disease and Memory Disorders Center at Baylor College of Medicine, and lead author of the report on solanezumab, said that the negative results in the primary outcomes indicate that the drug should not be approved as a treatment for mild-to-moderate Alzheimer’s disease. But she said a secondary analysis of the data suggests that the antibody therapy could be useful for those with mild disease.

“Three trials are under way to test the drug in patients with either mild or asymptomatic disease, she said. The study on mild disease involves people with sporadic AD and the asymptomatic studies are in carriers of mutations for familial AD and in people who have positive amyloid scans, Dr. Doody said. She said future research aimed at studying therapies in people with mild or asymptomatic disease needs to occur alongside the development of new drugs for those with full-blown illness.

“I never believed that there is going to be one mechanism that works against Alzheimer’s,” Dr. Doody said, but rather there will be combination drug therapy, as is the case with HIV and cancer. “There will be many different drugs and we will have to tailor their use depending on the stage of disease.”

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The two drugs being reported on target amyloid in different ways, she noted. Bapineuzumab binds aggregate amyloid beta, including binding to plaques, while solanezumab binds soluble amyloid beta. In addition, the drugs bind amyloid beta at different locations.

“We think solanezumab was binding soluble amyloid in the brain as well as in the blood,” Dr. Doody said. •

**Alzheimer’s Trials**

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