RESEARCH SUMMARY

Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease

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CLINICAL PROBLEM

The use of monoclonal antibodies developed to target different amyloid-beta (Aβ) protein species in patients with Alzheimer's disease has had mixed results in clinical trials. Trials in which amyloid plaques fell below the threshold for amyloid positivity showed cognitive and functional benefits, but trials in which removal of amyloid plaques was incomplete showed little to no benefit. Gantenerumab is a subcutaneously administered, fully human, anti-Aβ IgG1 monoclonal antibody with highest affinity for aggregated Aβ.

CLINICAL TRIALS

Design: Two phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trials — GRADUATE I and GRADUATE II — tested the clinical and biologic effects and safety of gantenerumab in participants with early symptomatic Alzheimer's disease.

Intervention: 1965 participants 50 to 90 years of age, who had mild cognitive impairment or mild dementia due to Alzheimer's disease and had evidence of amyloid plaque on positron-emission tomography or cerebrospinal fluid evaluation, were randomly assigned to receive gantenerumab or placebo for 116 weeks. The primary outcome was the change from baseline to week 116 in the Clinical Dementia Rating scale–Sum of Boxes (CDR-SB) score, which ranges from 0 to 18, with higher scores indicating greater cognitive impairment.

RESULTS

Efficacy: The use of gantenerumab led to an amyloid plaque burden that was lower than that with placebo but remained elevated; amyloid-negative status was attained in about one quarter of participants receiving gantenerumab. Gantenerumab treatment was not associated with slower clinical decline.

Safety: Amyloid-related imaging abnormalities with edema or hemosiderosis were more common after treatment with gantenerumab. Mortality was similar across trial groups.

LIMITATIONS AND REMAINING QUESTIONS

- Protocol differences limit comparisons with other trials of monoclonal antibodies for Alzheimer's disease.
- Racial diversity was low in the U.S. trial population.

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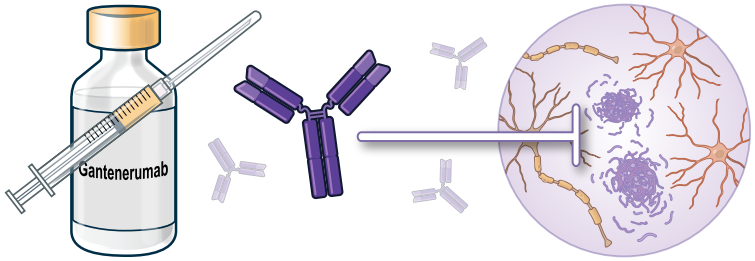
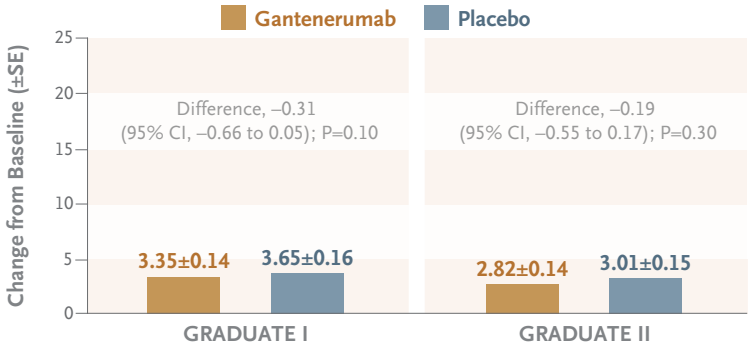
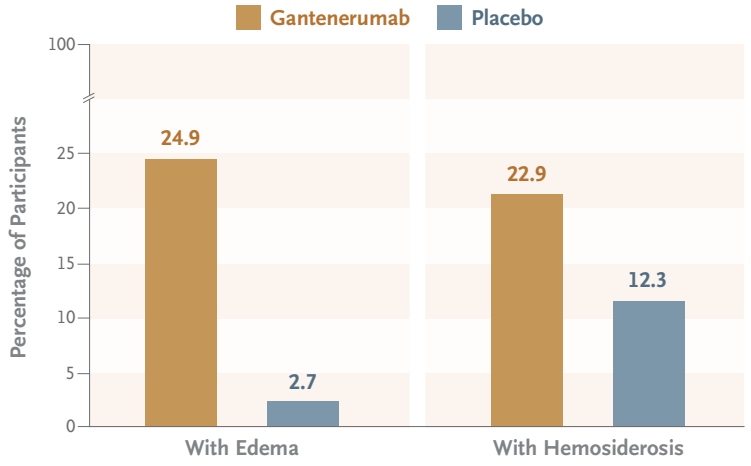


Change in the Clinical Dementia Rating Scale–Sum of Boxes Score



Amyloid-Related Imaging Abnormalities



CONCLUSIONS

Among participants with early symptomatic Alzheimer's disease, treatment with the antiamyloid antibody gantenerumab did not lead to slower cognitive decline than placebo over a period of 116 weeks.