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ALZHEIMER DISEASE

Anti-Aβ antibody treatment shows promise in Alzheimer disease

> We found a robust … reduction in amyloid burden

The antibody aducanumab can clear amyloid-β (Aβ) plaques from the brains of patients with prodromal or mild Alzheimer disease (AD), according to interim results of a phase Ib trial. Indications of concurrent slowing of cognitive decline suggest that aducanumab could offer a disease-modifying therapy for AD.

Aducanumab is a human antibody that selectively binds to Aβ aggregates — both soluble oligomers and insoluble fibrils. Work in mice has shown that the antibody can cross the blood–brain barrier and clear Aβ aggregates. Building on these findings, Alfred Sandrock and colleagues developed the PRIME trial to assess the safety and tolerability of aducanumab in humans, and its ability to clear Aβ plaques from human brains.

"By virtue of its specificity, aducanumab preferentially recognizes parenchymal amyloid deposits rather than vascular amyloid," explains Sandrock. "We hoped that this specificity would allow for higher doses to be used while avoiding amyloid-related imaging abnormalities (ARIA), a complication related to amyloid removal from blood vessels."

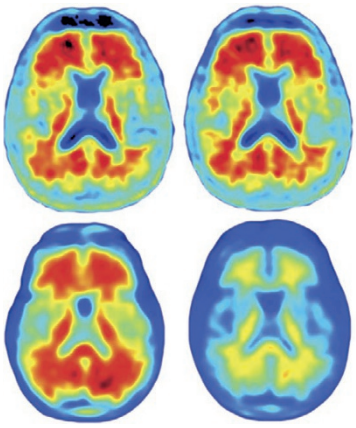
The trial involved 165 patients with prodromal or mild AD confirmed by Aβ PET. The patients were randomly assigned to receive either a placebo or aducanumab at doses of 1, 3, 6 or 10 mg/kg, once per month for 1 year.

Amyloid PET at the end of the trial revealed a significant effect of 3, 6 and 10 mg/kg aducanumab. "We found a robust time-dependent and dose-dependent reduction in amyloid burden," says Sandrock.

The investigators also assessed the effects of aducanumab treatment on cognitive function with the Mini Mental State Examination and Clinical Dementia Rating — Sum of Boxes. Insufficient power prevented definitive conclusions to be drawn, but the test scores suggested that aducanumab treatment slowed cognitive decline.

"The slowing of cognitive decline was correlated with the degree of lowering in amyloid burden," explains Sandrock. "The robust reduction in amyloid burden is probably the key reason for the hint of clinical efficacy on the exploratory cognitive endpoints."

Despite the specificity of aducanumab, ARIA developed in a number of treated participants, and was more common with higher doses of antibody. Nevertheless, 56% of participants who developed ARIA–vasogenic oedema continued treatment, and the condition resolved within 4–12 weeks. The only other severe adverse event reported was superficial siderosis of the CNS, which developed in six individuals.



Amyloid PET imaging at baseline (left) and 1 year (right) showed that a placebo had no effect (top), but 10 mg/kg aducanumab reduced amyloid burden (bottom). Reproduced with permission from Nature Publishing Group © Sevigny *et al.* *Nature* **537**, 50–56 (2016).

Sandrock says that the findings justify further investigation of aducanumab in the treatment of AD, and he and his colleagues are currently enrolling participants for phase III trials. "If the phase III studies confirm that aducanumab treatment slows the cognitive decline in patients with AD, we will have found a disease-modifying therapy."

Ian Fyfe

ORIGINAL ARTICLE Sevigny, J. *et al.* The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature* **537**, 50–56 (2016)