Nature Reviews Neurology **8**, 414 (2012); published online 10 July 2012; doi:10.1038/nrneurol.2012.128

ALZHEIMER DISEASE

Amyloid-β immunotherapy CAD106 passes first safety test in patients with Alzheimer disease

The immunotherapy CAD106, which comprises the N-terminal of amyloid-β (Aβ) peptide, has recently completed a double-blind placebo-controlled phase I trial in patients with Alzheimer disease. The drug was found to be safe and to generate an Aβ-specific antibody response, paving the way to future efficacy studies.

> "The drug was found to be safe and to generate an Aβ-specific antibody response..."

A previous phase II trial of another Aβ-targeted immunotherapy, AN1792, was suspended early as the treatment caused meningioencephalitis in 6% of treated patients. This adverse event was thought to be caused by a T-cell response to AN1792, as the drug consisted of full-length Aβ, which contains T-cell epitopes.

"As earlier trials failed owing to adverse effects, it was necessary to modify the method of vaccination," comments Bengt Winblad, who led the latest trial. By immunizing patients with CAD106, which contains B-cell but not T-cell epitopes, the researchers hoped to induce a purely beneficial immune response.

The study lasted 52 weeks plus a 2-year follow-up period, and involved two cohorts of patients with mild to moderate Alzheimer disease at two centres in Sweden. In cohort one, 31 patients were randomly assigned to receive three subcutaneous injections of 50 μg CAD106 or placebo at weeks 0, 6 and 18. Having established the safety and tolerability of this dosing regimen, patients in cohort two ($n = 27$) were assigned to three injections of 150 μg CAD106 or placebo at weeks 0, 2 and 6.

The most commonly reported drug-associated adverse effects were nasopharyngitis and injection-site erythema. Overall, nine patients experienced serious adverse events, none of which was thought to be related to CAD106.

Importantly, 67% and 82% of treated patients in cohorts one and two, respectively, had serum Aβ-specific IgG antibody titres that met the threshold for being classed as responders. "These patients developed antibodies to Aβ in a concentration probably sufficient to reduce the toxic effect in the brain," says Winblad.

Drug treatment did not reduce levels of Aβ or tau in the cerebrospinal fluid, but larger studies are required to detect any effect on disease biomarkers. A phase II trial of CAD106 is currently under way.

Katie Kingwell

Original article Winblad, B. *et al.* Safety, tolerability, and antibody response of active Aβ immunotherapy with CAD106 in patients with Alzheimer's disease: randomised, double-blind, placebo-controlled, first-in-human study. *Lancet Neurol.* **11**, 597–604 (2012)