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Active immunotherapy for Alzheimer's disease

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Alzheimer's disease is the most common cause of dementia globally, affecting about 36 million people at present and with about 115 million people expected to have the disease by 2050.[1] It is one of the most important health care, social, and economic challenges of the 21st century. Available treatments have minimal or no effect on the course of the disease. Many novel therapeutic strategies are being developed, with active and passive immunisation being among the most advanced approaches.[2–5] The neuropathology of Alzheimer's disease consists of the accumulation of amyloid β (Aβ) as amyloid plaques and cerebral amyloid angiopathy (CAA), as well as the accumulation of phosphorylated tau as neurofibrillary tangles. This pathology progresses over many years before individuals become symptomatic. The Aβ peptide is heterogeneous at both its amino and carboxyl termini, extending mainly to 42 aminoacids when deposited in plaques and 40 aminoacids when in CAA deposits. The most toxic forms of Aβ and tau are thought to be oligomeric. In 2002, one of the first active immunisation clinical trials (of AN1792),[2–5] which used full length aggregated $Aβ_{1–42}$ as an immunogen, was stopped when 6% of vaccinated patients developed meningoencephalitis. This complication was thought to be due to excessive T-helper (Th)-1-mediated inflammation, whereas the amyloid-reducing effects are mainly linked to humoral Th2-related immunity.[2–5]

10 years later, in this issue of *The Lancet Neurology*, Bengt Winblad and colleagues[6] describe the results of the first active immunisation phase 1 clinical trial since that of AN1792. For this second-generation Aβ vaccine (CAD106), a small Aβ fragment ($Aβ_{1–6}$) that is a B-cell epitope was used coupled to an adjuvant carrier formed by multiple copies of the coat protein of bacteriophage Qβ. Such an Aβ immunogen avoids the Th2-related T-cell epitopes present in full length $Aβ_{1–42}$, reducing the possibility of encephalitis as a complication. Winblad and colleagues enrolled patients with Alzheimer's disease who had a mini-mental state examination score of 16–26. Patients were randomly allocated either to three injections of 50 mg CAD106 (24 patients in cohort one) or 150 mg CAD106 (22 patients in cohort two) or to placebo (seven patients in cohort one and five in cohort two). The study-period was 52 weeks, with a 2-year follow-up period. In cohort one, 18 (75%) patients who received CAD106 developed anti-Aβ IgM titres and 16 (67%) developed anti-Aβ IgG titres; in cohort two, 22 (100%) patients developed anti-Aβ IgM titres and 18 (82%) developed anti-Aβ IgG titres. Although nine patients reported serious adverse reactions, none was thought to be related to the immunogen. No cases of meningitis, meningoencephalitis, or vasogenic oedema were detected clinically or by use of MRI during the trial period or in the 2-year follow-up period. CAD106-treated patients did not show statistically significant differences in CSF biomarkers compared with placebo but differences were seen in cohort two in CAD106-treated patients compared with those

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receiving placebo for free plasma $A\beta_{1–40}$. The study was not powered to show any clinical differences between CAD106-treated and control patients.

Many studies in transgenic mouse models of Alzheimer's disease have shown that both active and passive immunisation can drastically reduce amyloid deposition and prevent cognitive decline.[4,7] However, for highly successful immunotherapy for patients with Alzheimer's disease several problems need to be overcome, including avoidance of excessive cell-mediated immunity, reduction of CAA deposition, and the addressing of tau-related pathology, as well as identification of the most appropriate therapeutic target. Clinical and restricted autopsy data from the earlier active immunisation trials show a very small cognitive benefit despite amyloid plaque reductions.[2–5] These studies have shown that tau-related pathology and CAA were not reduced effectively. Such data have led to the suggestion that for Aβ-targeted vaccination to be clinically effective it needs to be started much earlier in the disease process, perhaps even before the onset of clinical symptoms. Alternatively, the direct targeting of tau-related pathology might be essential, because it correlates much better with clinical symptoms than do amyloid deposits.[8] Another point of view is that because Aβ and tau oligomers could be a main cause of Alzheimer's disease pathology, the targeting of their shared abnormal conformation as an immunomodulatory treatment is the best approach.[9] An additional consideration in the assessment of the likely future clinical success of CAD106 is that a substantial percentage of plaque Aβ in human beings is amino-terminally truncated and will be missing part or all of the $A\beta_{1–6}$ epitope; whether these modifications would affect a therapeutic response is unclear.[10]

Development of an immunotherapy that can delay Alzheimer's disease onset by 5 years would reduce the prevalence of the disease by half, and delaying onset for 10 years would almost eradicate symptomatic Alzheimer's disease.[11] This new second-generation vaccine comes as a welcome and promising addition to available evidence on what will probably be a long road to the ultimate successful immunotherapy. With the growing societal and governmental recognition of the importance of improving Alzheimer's disease treatment, later chapters to this evolving story of active vaccination for Alzheimer's disease will hopefully come faster than at 10-year intervals.

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